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THE MEASUREMENT OF CORONARY BLOOD FLOW, OXYGEN CONSUMPTION, AND EFFICIENCY OF THE LEFT VENTRICLE IN MAN

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THE introduction of the nitrous oxide method by Kety and Schmidt[1] has made it possible to determine the cerebral blood flow in dog and man. Eckenhoff and Goodale and their associates[2,3] have recently adapted this method for the measurement of coronary blood flow in the dog by collecting coronary venous blood through a catheter inserted into the coronary sinus. Catheterization of the coronary sinus in man has been successfully performed in a large series of cases.[4] It therefore seemed feasible to attempt the measurement of coronary blood flow in the human heart using the nitrous oxide method. This report describes the technique of coronary sinus catheterization and the determination of coronary blood flow in man. The findings will be discussed with reference to the extraction and consumption of oxygen and the liberation and utilization of energy in the normal and the diseased heart.

Anatomical Considerations.—The coronary sinus of man is situated in the posterior sulcus of the heart. It extends from the end of the great cardiac vein to its opening into the right auricle. Valves may be situated at its proximal and distal ends. The valve of Vieussens is at the entrance of the great cardiac vein into the coronary sinus, and the valve of Thebesius, at the coronary ostium.[5] The Thebesian valve is frequently absent. Usually there are no valves in the trunks of these vessels. In addition to these major valves,

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smaller ones are often found at the orifices of the tributary veins. The major veins which contribute to the sinus are the great and middle cardiac veins, the marginal veins, and the vein of Marshall.[5]

The ostium of the coronary sinus is located at the junction of the lower and medial auricular walls (Fig. 1). It is flanked on one side by the auriculoventricular foramen and on the other by an endocardial fold, the Eustachian ridge.[5] The latter structure, which is the rudiment of the right sinus valve, is subject to numerous variations. In the adult heart it may be more than 1.0 cm. in height (Fig. 1), or it may be a perforated netlike structure. It is possible that the Eustachian ridge is largely responsible for the difficulties encountered in the intubation of the coronary sinus.

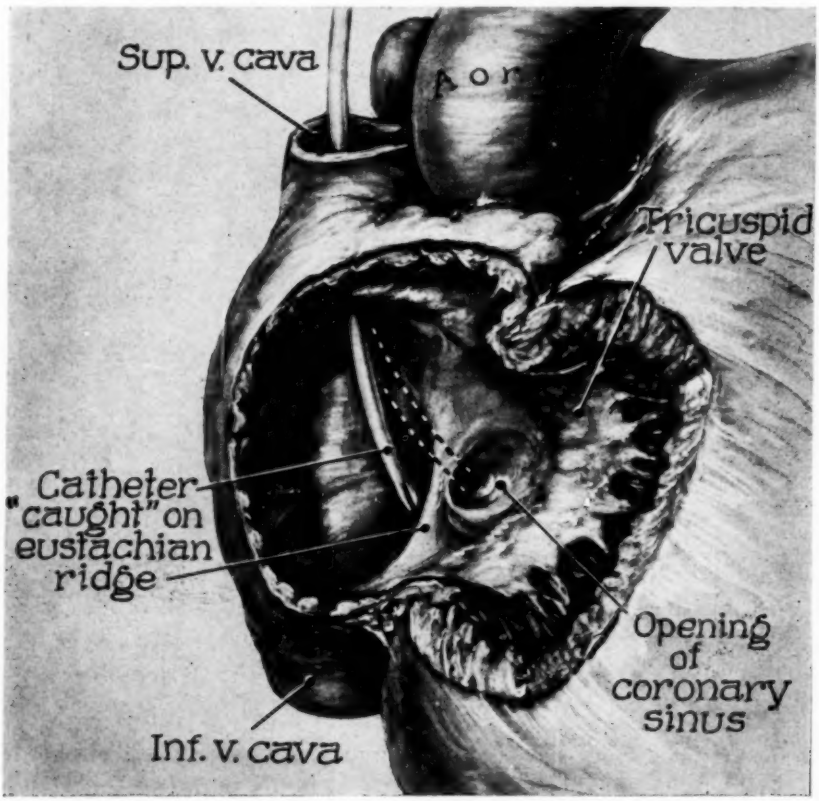

Fig. 1.—The anatomic relationships of the coronary sinus. Difficulties in intubating the coronary ostium are illustrated by showing the catheter caught on the Eustachian ridge.

PROCEDURES

Catheterization of the Coronary Sinus.—The anatomical considerations presented above indicate that catheterization of the coronary sinus in man presents problems which are not encountered during the catheterization of the coronary sinus in the dog or of the right ventricle in man. There are two

difficulties in the procedure. First, the introduction of the catheter into the coronary sinus from the right auricle may be impossible because of the presence of a prominent Eustachian ridge. Second, withdrawal of blood samples from the coronary sinus may be difficult as a result of occlusion of the catheter tip by valves or by the collapse of the walls of the sinus during withdrawal of blood.

To overcome these obstacles, certain modifications of the Cournand standard technique for intracardiac catheterizations in man[6] were introduced. The sampling difficulties mentioned have been largely overcome by use of a specially designed catheter which has been described elsewhere.[3] In addition, a stylette soldered to a Luer-Lok adapter was inserted into the catheter lumen, reaching to within 3 inches of the tip. This allowed the bend at the end of the catheter to remain intact, eliminating the danger of endocardial damage by a protruding wire. The stylette gave the catheter sufficient rigidity to prevent buckling, was airtight, and did not hamper withdrawal of blood.

Despite these improvements in technique, it has not been possible to catheterize the coronary sinus in more than 35 per cent of cases. If the catheter cannot be passed into the ostium of the coronary sinus within twenty minutes, further attempts are useless and should be abandoned. The low incidence of successful coronary catheterizations explains why only twenty-eight successful determinations were made during a two-year period.

Position of the Catheter in the Coronary Venous System.—Four criteria were used to determine that the catheter had entered the coronary sinus. They were: (1) the fluoroscopic position of the catheter, (2) the oxygen content of the coronary venous blood, (3) the pressure in the coronary sinus, and (4) absence of cardiac irregularities.

(1.) Fig. 2 shows the position of the catheter in the coronary sinus. In the anterior-posterior view a similar picture may be obtained with the catheter in the outflow tract of the right ventricle. Failure to guide the catheter into the pulmonary artery, however, suggested that the sinus had been entered. Further insertion of the catheter did not cause buckling, as it would in the right ventricle. It was often helpful to turn the patient into the right lateral position, where frequently a sharp angulation of the catheter could be seen at the coronary ostium. In the dog this observation has been found of great value.[3] In man, however, the lateral position was less informative because of variations in the position of the coronary sinus in dilated hearts.

(2.) The oxygen content of coronary venous blood is considerably less than that of mixed venous blood (Table I); therefore, it was often possible to confirm the position of the catheter in the sinus by comparing the color of the blood sample with that of mixed venous blood. If such a comparison is inconclusive, the blood should be analyzed immediately for its oxygen content. An oxygen content of less than 8 volumes per cent is indicative of coronary venous blood.

Fig. 2.—The x-ray appearance of the catheter in the coronary sinus in the anteroposterior position.

(3.) The systolic pressure in the sinus usually does not exceed 14 mm. Hg, whereas the normal systolic pressure in the right ventricle is usually 27 mm. of mercury.

(4.) Irregularities frequently occurred when the catheter tip passed the tricuspid valve or lay against a portion of the medial wall of the right ventricle Irregularity of the pulse has never been noticed with the catheter in the coronary sinus or the great cardiac vein.

The Measurement of the Coronary Blood Flow.—The principle of the nitrous oxide method outlined by Kety and Schmidt[1] and by Eckenhoff and his associates[2] was followed. However, several modifications were introduced to adapt the procedure to the measurement of coronary blood flow in man.

Administration of Nitrous Oxide.—Nitrous oxide was administered from a 10-liter anesthesia bag connected to a tank containing a mixture of 15 per cent

TABLE I. DATA ON BLOOD OXYGEN VALUES OF ARTERIAL, MIXED VENOUS, AND CORONARY VENOUS BLOOD

NO.	SUBJECT	SEX	AGE	HGB. (GM./100 C.C.)	O_2 CONTENT R.V. (VOL. %)	O_2 CONTENT C.S. (VOL. %)	O_2 CONTENT F.A. (VOL. %)	A-V O_2 DIFFERENCE (VOL. %)	
								CORONARY (F.A.-C.S.)	SYSTEMIC (F.A.-R.V.)
				GROUP I. NORMAL					
1	W. J.	M	31	13.4	12.9	3.9	17.1	13.2	4.2
2	R. E.	M	55	12.9	12.8	4.9	16.6	11.7	3.8
3	S. S.	M	33	15.0	15.6	6.9	18.9	12.0	3.3
4	I.F.	M	44	10.3	11.6	4.5	13.4	8.9	1.8
				GROUP II. ANEMIA					
5	J. B.	M	54	9.0	9.8	3.4	11.5	8.1	1.7
6	J. B	M	63	8.2	9.1	1.6	10.5	8.9	1.4
7	E. B.	F	21	8.8	7.2	1.7	10.8	9.1	3.6
				GROUP III. HYPERTENSION					
9	L. H.	F	68	11.7	11.0	5.3	14.7	9.4	3.7
10	M. L.	F	51	10.5	10.9	3.5	13.4	9.9	2.5
11	G. H.	M	56	13.4	15.0	4.5	17.5	13.0	2.5
				GROUP IV. COARCTATION OF THE AORTA					
12	D. M.	M	15	14.2	16.0	6.3	18.4	12.1	2.4
13	P. M.	M	18	14.5	16.3	2.4	18.9	16.5	2.6
14	L. W.	M	32	16.0	17.5	7.1	21.3	14.1	3.1
15	L. M.	F	12	12.6	13.5	2.6	16.2	13.6	2.7
16	C. L.	F	30	12.7	13.3	2.5	16.4	14.1	3.1
				GROUP V. CONGESTIVE FAILURE					
17	R. T.	F	37	15.4	13.4	4.7	19.9	15.0	6.3
18	V. A.	F	26	12.9	10.6	4.0	16.6	12.6	6.0
19	C. M.	F	63	15.9	13.6	3.2	18.9	15.7	5.3
26	A. E.	F	38	15.0	14.3	4.3	18.6	14.3	4.3
24	B. C.	M	64	13.1	9.8	3.2	15.6	12.5	5.6
27	W. W.	M	53	14.7	10.7	4.0	17.8	13.8	7.1
				MISCELLANEOUS					
				Aortic Insufficiency					
20	M. C.	F	35	12.2	12.6	4.0	15.6	11.6	3.0
				Aortic Stenosis and Insufficiency					
21	A. G.	M	27	14.1	14.4	6.2	18.1	11.9	3.7
				A-V Fistula					
23	J. K.	M	23	13.8	16.3	7.7	17.4	9.6	1.0
				Hyperthyroidism					
25	R. H.	M	46	10.8	10.6	4.7	13.4	8.9	3.0
				Myocardial Damage					
28	W. B.	M	65	7.2	6.5	3.1	9.6	6.1	3.0

R. V.—Right ventricle. C. S.—Coronary sinus. F. A.—Femoral artery.

nitrous oxide, 20 per cent oxygen, and 65 per cent nitrogen. A corrugated respiratory rubber tubing led fr. m this bag to a three-spigot valve and thence to metal T tube containing an inspiratory and expiratory flutter valve as well as a mouthpiece (Fig. 3). The mouthpiece was preferred to a respiratory mask since leakage was less frequently encountered. The patient was allowed to breathe the gas mixture for fifteen minutes to permit full equilibrium of the nitrous oxide with the tissues. After blood samples for oxygen content and nitrous oxide concentration at full saturation had been drawn, the mouthpiece and nose clip were quickly removed.

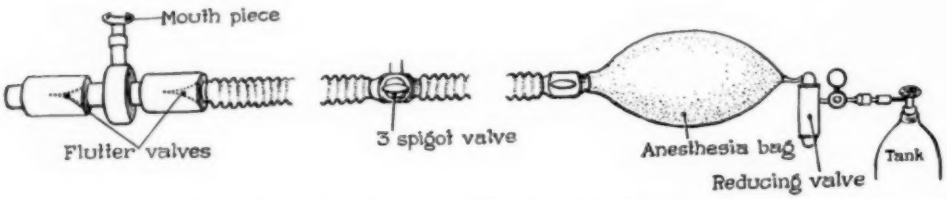

Fig. 3.—The respiratory system for administration of nitrous oxide.

When the method was carried out in this manner, the calculations were based upon a desaturation curve of nitrous oxide as suggested by one of us (W. G.). In the original method, blood samples were taken while the individual was breathing nitrous oxide, resulting in rising nitrous oxide levels. However, this frequently resulted in fluctuations of the nitrous oxide concentrations of the blood due to leakage around the mouthpiece or to respiratory irregularities. These errors were eliminated by use of the desaturation method. In order to calculate the amount of nitrous oxide given up by the heart, it was necessary to subtract the venous level after eight minutes from the venous level at full saturation. The other points on the curve were obtained by subtracting the nitrous oxide concentration of each individual sample from the nitrous oxide concentration at full saturation. This resulted in rising curves similar to those obtained by Kety and Schmidt and by Eckenhoff and his associates, who obtained their samples during the saturation period (Fig. 4).

Preparation of Syringes.—Fifteen dry Luer-Lok syringes of 10 c.c. capacity were autoclaved for sampling of arterial and venous blood, respectively. These were packed with metal sealing caps for the syringes, a beaker of 20 c.c. capacity, and a syringe containing 10 c.c. of Nujol. The set for sampling of arterial blood also contained the manifold described by Kety and Schmidt.[1] As soon as the position of the catheter in the coronary sinus had been ascertained, administration of nitrous oxide was begun and the syringes were prepared for sampling in the following manner:

One 10 c.c. syringe was filled with 5.0 c.c. of a 1.0 per cent heparin solution (Lederle). The oil syringe was emptied into the beaker, and the plunger of each of the remaining syringes was dipped into the oil, which was distributed along the syringe barrel by the plunger. From the heparin syringe, 10 drops of heparin

were introduced into each oiled syringe and distributed along the wall. The manifold was then assembled for collection of arterial blood and a heparin syringe was attached. No manifold was used to sample coronary vein blood.

Sampling of Blood.—The tissues overlying the brachial or femoral artery were infiltrated with 2.0 per cent procaine. An indwelling 19-gauge needle with obturator was then placed in the artery. The manifold system was filled with heparin. Several minutes before the end of the saturation period the obturator was removed and the needle was connected to the manifold with polythene tubing which had been sterilized in Zephiran and rinsed with saline solution.

Just before the end of the saturation period, two samples of both venous and arterial blood were collected, one for determination of nitrous oxide at full saturation and the other for analysis of the oxygen content.

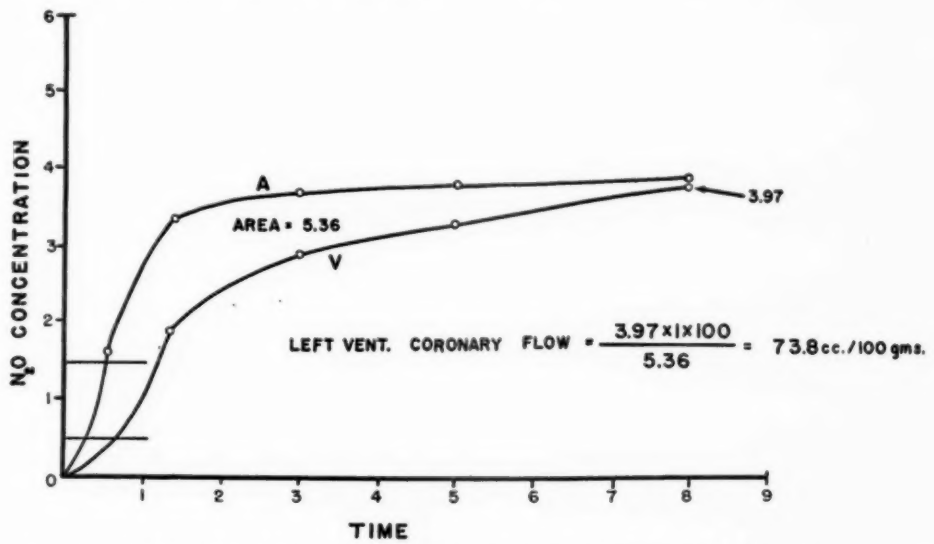

Fig. 4.—The arterial and coronary venous nitrous oxide curves obtained during desaturation. Rising curves are obtained by subtracting each sample from the nitrous oxide concentration at full saturation.

Calculations. — The coronary blood flow was calculated according to the method of Kety and Schmidt except for differences arising from the use of desaturation curves. A partition coefficient of 1 for human heart muscle was used.[2] The values obtained represented the blood flow per 100 grams of left ventricular muscle per minute.

The oxygen consumption per 100 grams of left ventricular muscle was obtained with the equation:

Oxygen consumption per 100 grams of left ventricular muscle per minute =
(arterial oxygen content volume per cent — coronary sinus oxygen content volume per cent) ×
left ventricular coronary flow per 100 grams left ventricular muscle per minute.

It is necessary at this point to discuss the validity of the various calculations involving the oxygen content of coronary venous blood.

It is generally recognized that coronary sinus blood is not true mixed coronary venous blood.[7] This fact, however, does not detract from the accuracy of determinations computed for 100 grams of cardiac tissue, since the oxygen consumption of and the blood flow through 100 grams of cardiac muscle are obtained only for that portion of the heart from which blood drains into the coronary sinus. It is apparent, however, that contamination of coronary venous blood with *mixed* venous blood will introduce an error. This may be suspected if arterial and coronary venous nitrous oxide concentrations do not approach each other after a desaturation period of eight minutes.

In the calculation of cardiac efficiency, which represents the ratio of work performed to the energy equivalent of the oxygen uptake (the energy cost), a series of assumptions will be made which will be discussed at this point.

1. Values for ventricular work and for energy cost must be obtained for identical portions of the heart. Since it is probable that coronary sinus blood consists of blood which has perfused left ventricular muscle,[8] the work/energy cost relationship must be calculated for the left ventricle only. It is conceivable, however, that with variations in the ventricular pressures, the coronary sinus contains blood from other portions of the cardiac muscle.[9] This introduces an appreciable error since then the energy cost and work are not related to the same portion of the heart.

2. In order to obtain the energy equivalent of the oxygen taken up by the heart muscle, a respiratory quotient of 0.82 was assumed. This assumption is based on the work of Macleod.[10] Several direct determinations of the respiratory quotient from coronary blood have given similar values.[11] Accordingly, each liter of oxygen consumed releases 2,059 kilogram-meters of energy. The figure thus obtained represents the energy cost per 100 grams of left ventricular muscle.

3. In calculating the relationship of left ventricular work to energy cost, the oxygen consumption of the entire left ventricular muscle must be obtained. This offers serious difficulties, since indirect estimations of the weight of the heart in situ and particularly of the left ventricular muscle must be considered as inaccurate. Smith[12] has compiled a chart relating heart weight, body weight, and sex in normal individuals. The mean values from this chart were used to obtain heart weights of individuals with normal left ventricular work. The left ventricular weight was assumed to be 53 per cent of the total heart weight.[12] Estimations of the left ventricular weight in the presence of cardiac hypertrophy may involve errors as large as 200 to 300 per cent. Consequently, no calculations have been made which utilize this estimate. Instead, the predicted normal left ventricular weight has been used with the understanding that this gives values for total left ventricular oxygen consumption which are lower than the correct values.

The oxygen consumption of the left ventricle was then obtained with the formula:

$$\textit{Oxygen consumption of the left ventricle (cubic centimeters of oxygen per minute)} = \frac{\textit{left ventricular weight}}{100} \times \textit{oxygen consumption per 100 grams.}$$

The efficiency of the left ventricular muscle was calculated according to the equation:

$$\textit{Mechanical efficiency (per cent)} = \frac{\textit{work of left ventricle (kilogram-meters per minute)}}{\textit{energy cost of left ventricle (kilogram-meters per minute)}}$$

The numerator of this equation was obtained using the formula of Starling[13]:

$$\textit{Work (kilogram-meters per minute)} = \textit{cardiac output (cubic centimeters per minute)} \times \textit{mean aortic pressure (cm.Hg)} \times 13.6.$$

No allowance was made in this calculation for the velocity energy, since this component represents less than 10 per cent of left ventricular work.[14]

These considerations indicate that values for the coronary blood flow and the oxygen consumptions per 100 grams of left ventricular tissue may be considered accurate under all circumstances. Conversely, in the hypertrophied heart, figures for the oxygen consumption of the whole left ventricle are too low, and hence the calculated efficiency is too high.

Selection of Patients.—Catheterization of the coronary sinus in man was begun only after observations on animals had shown that this procedure was without risk if certain precautions were taken.[3] In most instances cardiac catheterization was performed for diagnostic purposes and the left ventricular blood flow was measured after cardiac output had been determined. Consequently, most patients had cardiac abnormalities which required evaluation for surgical or medical therapy. The nature of the procedure was explained to the patient and his written consent was obtained.

In the subsequent paragraphs, patients will be divided into various groups (Tables I and II): Group I, four normal subjects with hemoglobin above 10 grams; Group II, three patients with postoperative hypochromic microcytic anemia (hemoglobin below 10 grams); Group III, five patients with essential hypertension (mean blood pressure above 100 mm. Hg); and Group IV, five patients with coarctation of the aorta. Group V included five patients with congestive heart failure resulting from mitral stenosis and insufficiency, and two with congestive failure due to arteriosclerotic heart disease. In addition to these groups, five patients with various cardiovascular disorders were studied. These included two patients with aortic stenosis and insufficiency, respectively, who showed no clinical or physiologic evidence of cardiac failure. The other patients were: one with an arteriovenous fistula of the femoral artery, one with hyperthyroidism, and one with electrocardiographic and clinical evidence of coronary insufficiency and severe anemia (hemoglobin 6.8 grams). The latter patient had had a coronary occlusion four years preceding the test.

TABLE II. DATA USED IN THE CALCULATION OF LEFT VENTRICULAR EFFICIENCY

NO.	SUBJECT	SEX	AGE	HGB. (GM./100 C.C.)	CARDIAC OUTPUT (C.C./ MIN.)	CARDIAC OUTPUT (C.C./ MIN./M.^{2})	AORTIC MEAN PRESSURE (MM. HG.)	L.V. WORK (KG.-METERS)	CORONARY FLOW (C.C./ 100 GM./MIN.)	OXYGEN EXTRACTION (VOL. %)	O_2 CONSUMPTION/ 100 GM./ MIN.	ENERGY COST L.V. (KG.-METERS)	EFFICIENCY (PER CENT)
						GROUP I. NORMAL							
1	W. J.	M	31	13.4	5,400	2,720	87	6.4	55	13.2	7.4	34.1	21.2
2	R. E.	M	55	12.9	4,020	2,440	95	5.2	70	11.8	8.3	22.5	23.1
3	S. S.	M	44	15.0	3,760	2,170	93	4.8	69	12.1	8.3	24.7	19.2
4	I. F.	M	44	10.3	5,150	2,860	93	5.6	66	10.9	7.2	22.8	24.5
						GROUP II. ANEMIA							
5	J. B.	M	54	9.0	4,700	3,070	97	6.2	63	8.1	5.1		
6	J. B.	M	63	8.2	8,000	4,570	90	9.8	95	8.9	8.5		
7	E. B.	F	21	8.8	5,220	3,160	77	5.5	84	9.1	7.7		
						GROUP III. HYPERTENSION							
9	L. H.	F	68	11.7	7,500	4,440	156	15.8	59	9.4	5.5		
10	M. L.	F	51	10.5	7,350	4,380	130	13.0	64	9.9	6.3		
11	G. H.	M	56	13.4	9,350	4,410	163	19.4	73	13.0	9.5		
						GROUP IV. COARCTATION OF THE AORTA							
12	D. M.	M	15	14.2	6,700	3,960	107	9.8	91	12.2	11.1		
13	P. M.	M	18	14.5	6,040	3,230	107	8.8	68	16.2	11.0		
14	L. W.	M	32	16.0	4,775	3,800	127	8.3	58	14.1	8.2		
15	L. M.	F	12	12.6	6,500	4,500	122	11.6	135	13.9	18.8		
16	C. L.	F	30	12.7	4,820	3,070	123	8.0	64	13.8	8.7		

						GROUP V. CONGESTIVE FAILURE							
17	R. T.	F	37	15.4	3,025	1,880	78	3.24	54	15.0	8.1	25.1	12.9
18	V. A.	F	26	12.9	3,070	1,890	90	3.76	61	12.6	7.8	21.9	17.1
19	C. M.	F	63	15.9	3,400	2,090	105	4.85	66	15.7	10.4	32.2	15.1
26	A. E.	F	38	15.0	3,800	2,320	82	4.2	75	14.3	10.4	28.8	14.8
24	B. C.	M	64	13.1	3,500	2,120	103	4.8	75	12.4	9.4	34.8	14.1
27	W. W.	M	53	14.7	3,320	2,100	73	3.3	52	13.8	7.2	22.5	14.6
						MISCELLANEOUS							
						Aortic Insufficiency							
20	M. C.	F	35	12.2	5,900	3,760	92	7.4	93	11.6	10.8		
						Aortic Stenosis and Insufficiency							
21	A. G.	M	27	14.1	4,100	2,180	80	4.5	70	11.9	8.5		
						Arteriovenous Fistula							
23	J. K.	M	23	13.8	20,590	11,700	65	18.2	84	9.6	8.1		
						Hyperthyroidism							
25	R. H.	M	46	10.8	8,700	5,300	90	10.6	85	8.9	7.5		
						Myocardial Damage and Anemia							
26	W. B.	M	65	7.2	8,000	5,100	85	10.0	58	6.0	3.5		

Special Techniques.—Blood oxygens were determined by the manometric method of Van Slyke and Neill.[15] The oxygen consumption was obtained from the oxygen and carbon dioxide content of expired air, which was collected in a Douglas bag over a period of one and one-half minutes. The oxygen in expired air was determined with the Pauling oxygen analyzer. The carbon dioxide was determined on the Haldane apparatus. Pressures were optically recorded with strain gauges. The mean pressure was obtained by planimetric integration of the area under the pressure curve.

RESULTS

The Oxygen Content and the Arteriovenous Oxygen Difference of Coronary Blood.—Table I shows that in the normal subjects the oxygen content of coronary venous blood varies from 3.9 to 6.9 vol. per cent. This finding agrees with the result of Eckenhoff and his associates[2] for the anesthetized dog. Studies in this laboratory on the unanesthetized dog reveal somewhat lower values.[16] The oxygen content of coronary sinus blood was considerably lower than that of mixed venous blood (Table I). The oxygen extraction ranged from 8.9 to 13.2 vol. per cent, with an average of 12 vol. per cent (Table I and Fig. 5).

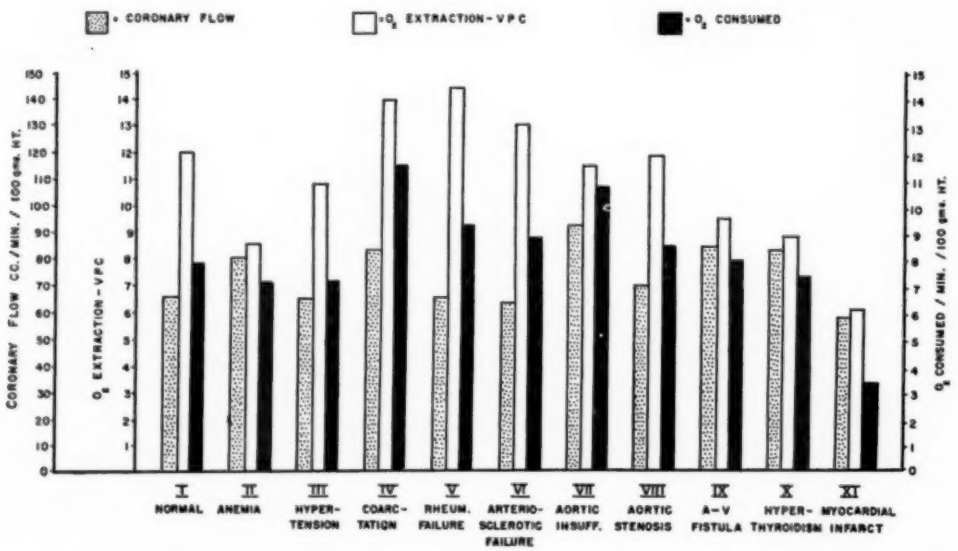

Fig. 5.—Summary of the average values for left ventricular coronary blood flow per 100 grams per minute, oxygen extraction, and left ventricular oxygen consumption per 100 grams per minute obtained in the various groups of patients studied.

In individuals belonging to Group II (anemia) the left ventricular oxygen extraction was smaller, varying from 8.1 to 9.1 vol. per cent, with an average of 8.7 vol. per cent (Table I and Fig. 5). The oxygen content of coronary sinus blood was 1.6 vol. per cent in two patients with a hemoglobin content of 8.2

and 8.8 grams, respectively (Table I). In these individuals the oxygen difference between femoral arterial and mixed venous blood was also significantly reduced (Table I).

It seemed noteworthy that the left ventricular extraction of oxygen in papatients with essential hypertension (Group III) was below normal, varying from 9.4 to 13 vol. per cent, with a mean of 10.8 (Table I and Fig. 5). It will be shown that this factor is responsible for decreased left ventricular oxygen consumption per 100 grams found in the patients of this group. The oxygen content of coronary sinus blood in these cases ranged from 3.5 to 5.3 vol. per cent.

In individuals belonging to Group IV (coarctation of the aorta) the oxygen extraction was significantly elevated, varying from 12.1 to 16.5 vol. per cent, with an average of 14 vol. per cent (Table I and Fig. 5). Since the coronary blood flow was normal or increased, the oxygen consumption was significantly elevated. The oxygen content of coronary sinus blood ranged from 2.4 to 7.1 vol. per cent (Table I).

In the patients with mitral stenosis and insufficiency (Group V) the oxygen extraction of left ventricular muscle was significantly elevated, ranging from 12.6 to 15.8 vol. per cent, with a mean of 14.4 vol. per cent (Table I and Fig. 5). The oxygen difference between peripheral arterial and mixed venous blood was also increased (Table I). The oxygen content of coronary sinus blood varied from 3.2 to 4.7 vol. per cent (Table I). The two patients in failure due to arteriosclerotic heart disease had an average oxygen extraction of 13.1 vol. per cent (Fig. 5). The oxygen content of coronary sinus blood averaged 3.6 vol. per cent (Table I).

In the two patients with aortic insufficiency and stenosis the oxygen extraction was 11.6 and 11.9 vol. per cent, respectively (Table I and Fig. 5). The oxygen content of coronary sinus blood was 4.0 and 6.2 vol. per cent (Table I). In the patient with the arteriovenous fistula the oxygen content of the coronary sinus blood was 7.7 vol. per cent, with an extraction of 9.6 vol. per cent (Table I and Fig. 5). The patient with hyperthyroidism had a coronary sinus oxygen value of 4.7 vol. per cent and an extraction of 8.9 vol. per cent (Table I and Fig. 5). The patient with coronary insufficiency and anemia had a coronary sinus oxygen content of 3.1 vol. per cent and an extraction of 6.1 vol. per cent (Table I and Fig. 5).

The Coronary Flow and the Left Ventricular Oxygen Consumption.—The left ventricular blood flow in the normal subjects (Group I) ranged from 55 to 70 c.c. per 100 grams per minute (Table II and Fig. 5), with a mean of 65 c.c., and the left ventricular oxygen consumption per 100 grams ranged from 7.2 to 8.3 c.c. per minute, with an average of 7.8. In the normal anesthetized dog the average left ventricular oxygen consumption was 9.5 c.c. per 100 grams per minute,[18] although the unanesthetized dog revealed considerably higher values.[16]

In patients with anemia (Group II) the left ventricular flow was increased (from 62.5 to 95 c.c. per 100 grams per minute, with a mean of 81 c.c.). Be-

cause of the marked decrease in oxygen extraction, however, the oxygen consumption was below normal, with a mean of 7.1 c.c. per 100 grams per minute (Table II and Fig. 5).

In patients with essential hypertension (Group III) the coronary flows were within normal limits, ranging from 59 to 73 c.c. per 100 grams per minute, with an average of 65 cubic centimeters. The left ventricular oxygen consumption per 100 grams was slightly below normal, averaging 7.1 c.c. per 100 grams per minute (Table II and Fig. 5). In contrast, patients with coarctation of the aorta (Group IV) showed a significant increase in the coronary blood flow and the left ventricular oxygen consumption. The left ventricular coronary flow (Table II and Fig. 5) ranged from 64 to 135 c.c. per 100 grams per minute, with a mean of 83 cubic centimeters. The highest flows in this group were recorded in the younger patients. The oxygen consumption per 100 grams of left ventricular tissue was also markedly elevated, the values ranging from 8.2 to 18.8 c.c. per 100 grams per minute, with an average of 11.6 (Table II and Fig. 5).

The left ventricular coronary blood flows in patients with congestive heart failure due to mitral stenosis and insufficiency were normal, ranging from 54 to 75 c.c. per 100 grams per minute, with a mean of 64 c.c. (Table II and Fig. 5). These values may be lower than the true flows because of the failure of the venous curve to approach the arterial as a single exponential function.[2] This could have been the result of the presence within the cardiac tissue of fat, which has a greater nitrous oxide capacity and consequently a longer saturation time than cardiac muscle. The increased oxygen extraction in these patients was responsible for the fact that the left ventricular oxygen consumption per 100 grams of cardiac tissue was slightly increased (Table II and Fig. 5). The left ventricular oxygen consumption in failure ranged from 8.1 to 10.4 c.c. per 100 grams per minute, with a mean value of 9.2 c.c. (Table II). These findings may not represent true values since the coronary flows were probably too low. However, even if the oxygen consumptions in these four patients were calculated for heart muscle which has been fully equilibrated with nitrous oxide, the values for oxygen consumption would still be less than those observed in the failing heart in vitro.[7] The significance of this finding will be discussed in a subsequent paragraph.

In the two patients suffering from arteriosclerotic heart disease with congestive failure the left ventricular oxygen consumption per 100 grams was 8.3 c.c. per minute (Table II and Fig. 5). The oxygen extraction was normal (13.1 vol. per cent).

In the patient with aortic insufficiency the left ventricular coronary blood flow was 93 c.c. per 100 grams (Table II and Fig. 5). This represents a marked increase above normal values (Table II and Fig. 5). Green and his co-workers[17] also found that the coronary blood flow in aortic insufficiency was markedly increased, provided that the mean aortic pressure was not lowered. The left ventricular oxygen consumption per 100 grams per minute was 10.8 (Table II). This represents a significant increase over the normal.

The coronary flow and the left ventricular oxygen consumption per 100 grams were slightly elevated in the patient with the arteriovenous fistula, being 8.4 c.c. per 100 grams per minute and 8.1 c.c. per 100 grams per minute, respectively (Table II and Fig. 5). In the patient with hyperthyroidism the left ventricular flow and the left ventricular oxygen consumption were only slightly increased, being 84.5 c.c. per 100 grams per minute and 7.5 c.c. per 100 grams per minute, respectively (Table II and Fig. 5). This is surprising since the rise in the oxygen consumption per unit weight should be at least proportional to the total metabolism, which was markedly elevated (+50). In contrast, the left ventricular coronary flow in the patient with aortic stenosis was within normal range, being 70 c.c. per 100 grams per minute (Table II and Fig. 5). This patient had severe anginal pain on exertion, but was symptom free at rest. Apparently the coronary flow, though adequate at rest, could not increase sufficiently during exercise to supply the muscle with an adequate amount of oxygen. The oxygen consumption per 100 grams was within normal limits, being 8.5 c.c. per minute (Table II and Fig. 5).

The left ventricular coronary blood flow in the patient with coronary insufficiency and anemia was 58 c.c. per 100 grams per minute (Table II and Fig. 5). Since the oxygen extraction was only 6.05 vol. per cent, the oxygen consumption per 100 grams of ventricular muscle was 3.48 c.c. per minute. The extremely low values for the coronary flow and left ventricular oxygen consumption are particularly surprising in view of the elevated cardiac output, which was 8,000 c.c. per minute. It was apparent that the left ventricular oxygen consumption, determined by coronary sinus catheterization, was inadequate for the left ventricular work. Therefore, it must be surmised that the coronary sinus contained blood which had perfused scar tissue rather than healthy myocardium. This conclusion is supported by the electrocardiographic and clinical evidence of myocardial damage.

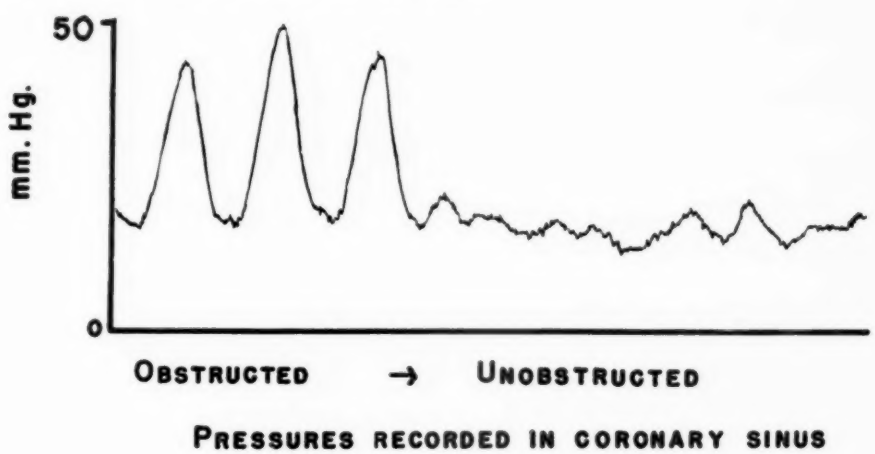

Fig. 6.—An optically recorded pressure tracing from the coronary sinus. The high pressures were obtained when the catheter was obstructing the outflow from the great cardiac vein. The arrow indicates the point at which the withdrawal of the catheter relieved the obstruction.

TABLE III. CORONARY SINUS PRESSURES (Mm. Hg)

SUBJECT	CORONARY SINUS	RIGHT AURICLE
Group I		
W. J.	14/9	
R. E.	13/10	
S. S.	15/6	
E. M.*	24/9	18/9
C. M.*	12/5	7/2
G. R.*	19/9	
B. F.*	18/14	16/13
C. S.*	15/7	
A. W.*	14/12	13/12
U. B.*	17/15	9/8
M. L.*	18/12	
Average	16/8	12/9
Group II		
J. B.	8/0	
J. B.	11/10	
Average	9/5	
Group III		
G. H.	14/6	
M. L.	11/4	
L. H.	11/4	
Average	12/6	
Group IV		
L. W.	11/4	
Group V		
R. T.	18/14	17/14
V. A.	28/15	
B. C.	28/20	
C. M.	10/7	
F. P.*	28/22	
Average	26/16	17/14

*Coronary flow not measured.

Coronary Sinus Pressure.—Pressures recorded from the coronary sinus show that in Group I the average systolic pressure was 16 mm. Hg; the average diastolic pressure, 8 mm. Hg (Table III). These findings confirm those reported in a previous communication.[4] Smaller values were obtained in Group II.

In contrast to these findings were those obtained in the patients with cardiac failure. Here the average systolic pressure was 21 and the average diastolic pressure 18 mm. of mercury.

A typical pressure tracing, recorded from the coronary sinus, is illustrated in Fig. 6. This tracing shows two different patterns; one follows closely the typical tracing obtained from the right auricle of man.[19] Two positive waves can be recognized. It is probable that these peaks correspond to the *a* and *c* waves seen in right auricular pressure tracings and are the result of auricular and ventricular contractions, respectively.

A different pattern was obtained in this same patient when the catheter tip was deeply introduced into the coronary sinus (Fig. 6). In this instance, systolic and diastolic pressures were significantly elevated and only one sharp peak, which closely followed the left ventricular ejection period, was recorded. It is possible that this pattern resulted from venous obstruction by the catheter, which permitted the transmission of aortic pressure waves through the capillary bed. Similar results have been obtained in dogs after obstruction of the coronary sinus with the catheter.[3]

It is, therefore, considered likely that the coronary sinus has no unique pressure pattern and that the observed tracings represent transmission of either auricular or aortic pressure waves.

DISCUSSION

Catheterization of the coronary sinus in man is a difficult procedure. This is primarily the result of anatomical variations in the structure of the right auricule, such as, for example, the presence of an elevated Eustachian ridge (Fig. 1). Although the incidence of successful catheterization of the coronary sinus can be increased by special technical improvements, only 25 per cent of all attempted catheterizations are successful. Despite these technical difficulties, catheterization of the coronary sinus had led to no untoward consequences.

In the evaluation of results presented in this paper, particular emphasis should be placed on a careful differentiation between data calculated directly and those obtained through assumptions. Thus, values for the coronary blood flow through left ventricular muscle and the oxygen consumption per 100 grams of left ventricular tissue may be considered accurate. The fact that coronary sinus blood is not true mixed coronary venous blood does not detract from the accuracy of these determinations, since they obtain only for that portion of the heart from which blood drains into the coronary sinus. Calculations of oxygen consumption of the entire left ventricle and its mechanical efficiency, however, involve estimations of left ventricular weight. This can be obtained only indirectly from tables relating heart weight and body weight, and from the assumption that left ventricular muscle comprises a constant fraction of the total heart weight.[12] It is therefore obvious that figures for the left ventricular energy cost and mechanical efficiency must be approximations. It is probable that calculations for the efficiency of the normal left ventricle are close to the actual values since the weight of the normal left ventricle may be estimated from the tables of Smith[12] with considerable accuracy. However, estimation of the weight of the hypertrophied or dilated left ventricular muscle cannot be made. For these reasons, only calculations of the efficiency of Groups I and V are included. Using maximal normal weights, certain trends in the direction of left ventricular efficiency may be estimated in congestive failure. As was pointed out in a previous section, the use of normal heart weights gives

values for the total left ventricular energy cost which are too low for the hypertrophied heart. Consequently, a high efficiency is not significant. On the other hand, a low efficiency obtained in hypertrophied hearts is of great significance, since the actual efficiency must be even lower. This is the case in congestive failure.

The results indicate that in the normal heart the oxygen content of coronary venous blood is considerably lower than that of mixed venous blood (Table I). Consequently, the coronary arteriovenous oxygen difference is higher than the difference between systemic and mixed venous blood (Table I). The left coronary ventricular blood flow in the normal ranges from 55 to 70 c.c. per 100 grams per minute (Table II and Fig. 5). Similar figures were previously obtained by Eckenhoff and his associates[2] in the anesthetized dog. Experiments undertaken in this laboratory indicate that the left ventricular coronary blood flow and left ventricular oxygen consumption per 100 grams are twice as great in unanesthetized dogs.[23] It is probable, therefore, that variations in the experimental conditions are largely responsible for the discrepancies observed.

In anemic subjects (Group II) the coronary arteriovenous oxygen difference and the oxygen consumption per 100 grams is reduced (Tables I and II and Fig. 5), while the coronary blood flow is slightly elevated (Table I and Fig. 5). This is of interest since it indicates that the increase in coronary blood flow is insufficient to compensate for the reduction in the coronary arteriovenous difference. Most individuals belonging to this group were only mildly anemic and only one had increased cardiac output (Subject 6, Table II). It is possible that in severe anemia the changes in coronary blood flow are greater. The oxygen content of coronary sinus blood in Patient E. B. (Table I) is only 1.5 vol. per cent. This individual suffered from anginal pain appearing on exercise. Since in this patient the oxygen extraction by the heart muscle is already maximal at rest, the heart must rely entirely on changes in coronary blood flow to fulfill its increased oxygen demand during exertion. Once the coronary flow has reached its upper limit, no further increase in oxygen consumption of the heart is possible. This results in relative cardiac anoxia and may lead to anginal pain.

In patients with essential hypertension (Group III) the oxygen extraction, the oxygen consumption per 100 grams of left ventricular tissue, and the left ventricular coronary blood flow per 100 grams are within normal limits (Tables I and II and Fig. 5). The observation that the coronary blood flow is normal in the presence of increased mean aortic pressure indicates that the vascular resistance in the coronary bed is increased. This finding contrasts with that obtained by Gregg[8] on the anesthetized dog. This investigator showed that when the blood pressure rose as a result of clamping of the aorta, the coronary minute volume increased with the blood pressure, regardless of changes in cardiac rate and output. The discrepancy between these results suggests an increase in the resistance in the coronary vascular bed of patients with essential hypertension. It is apparent that as a result of cardiac hypertrophy the total

left ventricular oxygen consumption is increased, although the oxygen consumption per unit weight is normal (Fig. 7). Evans,[14] among others, has shown in the heart-lung preparation that a sudden increase in the vascular resistance produced a rise in oxygen consumption per unit of left ventricular weight.

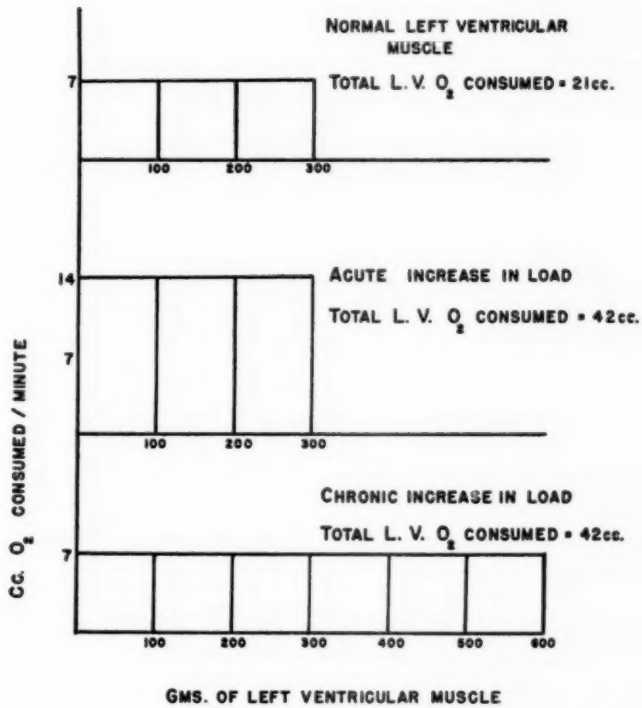

Fig. 7.—Comparison of the response of heart muscle to acute and chronic increase in load. The data for the response to acute increase represent theoretical values similar to those obtained in acute experiments in the heart-lung preparation. The data for the response to chronic increase in load are taken from Group III, assuming a left ventricular weight of 600 grams. It may be seen that in contrast to acute increase in load, a chronic increase results in a rise in the total oxygen consumption while the oxygen consumption per unit of weight remains constant.

In individuals with coarctation of the aorta (Group IV), on the other hand, the average arteriovenous oxygen difference, the left ventricular coronary blood flow per 100 grams, and the cardiac oxygen consumption per 100 grams of left ventricular tissue are markedly elevated (Tables I and II and Fig. 5). Tables I and II illustrate, however, that the coronary blood flow is greatest in the younger individuals. The oxygen extraction and the oxygen consumption per 100 grams of left ventricular tissue, on the other hand, are increased in all patients with this malformation (Tables I and II). These findings differentiate the coronary hemodynamics in coarctation from those in essential hypertension where the oxygen consumption per 100 grams of left ventricular muscle is normal. The observation that the coronary blood flow in the younger individuals of this group is elevated may be due to the smaller heart size. This

would increase the left ventricular coronary flow per unit weight, while the flow through the whole left ventricular muscle remains normal. Spencer and his associates[16] have found a very close relationship between body weight and coronary flow per unit of left ventricular tissue. The increase in left ventricular oxygen consumption per 100 grams found in all patients with coarctation of the aorta is of interest from another standpoint. According to Starling,[20] increased diastolic volume results in increased fiber length and consequently in an increased left ventricular oxygen consumption. It is possible, therefore, that in coarctation the diastolic volume of the left ventricle is greater than in compensated forms of essential hypertension. This hypothesis is supported by the finding that pulmonary hypertension has been present in all cases of coarctation studied in this laboratory. This may have been the result of increased diastolic blood volume in the left ventricle.

In the six patients with congestive failure due to arteriosclerotic heart disease and mitral stenosis and insufficiency (Group V) the oxygen consumption per 100 grams of left ventricular tissue is slightly elevated. The left ventricular diastolic volume, on the other hand, is probably increased. This is supported by fluoroscopic evidence of left ventricular enlargement and clinical signs of mitral regurgitation. Starling and Visscher,[20] investigating the mechanism of heart failure in vitro, found that the increase in diastolic volume led to a proportional increase in the oxygen consumption per unit weight. It is therefore difficult to explain why only a slight increase in the oxygen consumption per unit weight is present in the patients of this group.

The elevation of the coronary blood flow in the patients with aortic insufficiency and arteriovenous aneurysm (Fig. 5) confirms the finding of Green[17] in experimental aortic insufficiency and arteriovenous fistula. The same investigator found that the coronary flow in severe artificially produced aortic stenosis was markedly reduced. In the patient with aortic stenosis (A. G., No. 2, Table II and Fig. 5), however, the left ventricular coronary blood flow was normal at rest. The observation that this individual had severe anginal pain on exertion, but was symptom free at rest, indicates that the coronary flow could not increase sufficiently during exertion.

A consideration of the results obtained in the patient with myocardial damage is especially important since it raises the question whether or not coronary sinus blood can be considered as representative of blood which has coursed through left ventricular tissue. It was pointed out in a previous paragraph that blood withdrawn from the coronary sinus is assumed to be representative of blood which has perfused left ventricular muscle. In the presence of scar tissue, however, a fraction of coronary sinus blood will not have coursed through normal myocardium and the above assumption will not be valid. In this case, values obtained are probably lower than those for unaffected myocardium, since the scar tissue of the infarct represents an area of low flow and decreased oxygen uptake. It is important to emphasize, however, that the presence of scar tissue can be suspected by failure of the arterial and venous nitrous oxide curves to reach equilibrium within eight minutes.

An analysis of pressure tracings obtained from the coronary sinus shows no characteristic pattern (Table III and Fig. 5). Two types of curves are obtained (Fig. 6), one resembling an auricular, the other a dampened aortic tracing. The latter is obtained when the catheter tip is inserted deeply into the sinus, and probably obstructs the lumen.

The average systolic pressure in the unobstructed coronary sinus varies from 19 to 12 mm. Hg (Table III). In the patients with congestive failure, elevation of the right auricular pressure results in increase in coronary sinus pressure (Table III).

Although the data collected in this report are not numerous enough to permit statistical analysis, they represent two years of observations on the use of a new method. Technical difficulties in the method prevented the study of a larger series of patients. Certain trends are noticeable, however, which will be discussed at this point.

An examination of the relationship between cardiac output and coronary flow reveals some correlation in normal individuals and in the patients with postoperative anemia (Fig. 8). Excellent correlation has been found in the heart-lung preparation and in the normal unanesthetized dog.[21,16] In patients, however, in whom the cardiac output is elevated over long periods of time, as, for example, in arteriovenous fistula or in hyperthyroidism, the coronary blood flow per unit weight is within normal limits (Fig. 5).

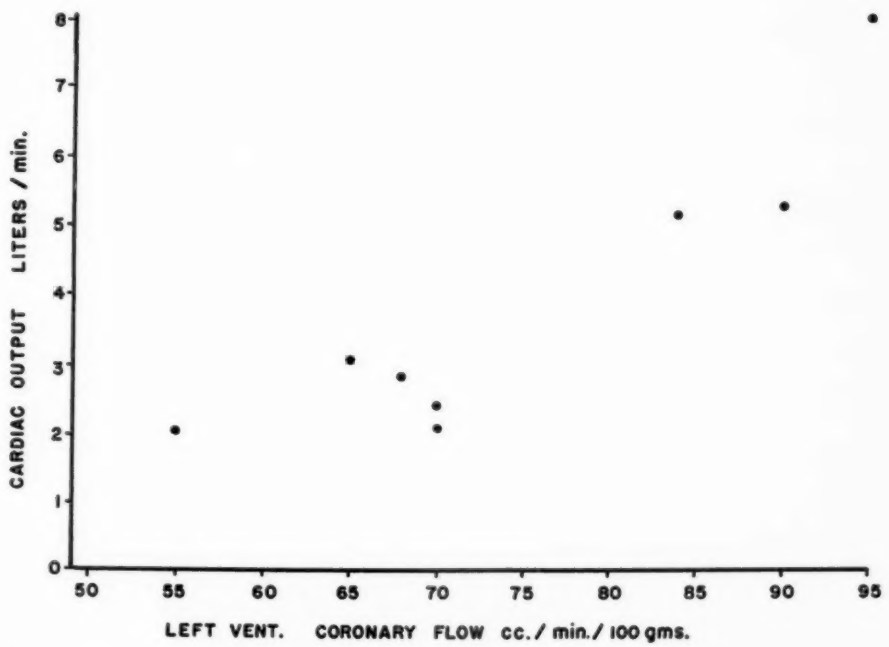

Fig. 8.—The relation between cardiac output and left ventricular coronary flow per unit weight of hearts of normal and acutely anemic individuals (Groups I and II). It can be seen that in these non-hypertrophied hearts the left ventricular coronary flow varies directly with the cardiac output.

In the patients of this series in whom the left ventricular load is elevated as a result of essential hypertension or arteriovenous fistula, the oxygen consumption per unit of left ventricular work remains normal. Starling and Visscher[20] among others demonstrated that an increase in load due to increased venous filling or to a rise in resistance results in a rise in the oxygen consumption of the heart. They demonstrated that this was the result of increased diastolic fiber length. Since the weight of the isolated heart remains constant as the load increases, the oxygen consumption per unit weight increases proportionally. The finding obtained in the patients with essential hypertension and arteriovenous fistula demonstrates a different response of the heart to chronic increase in load from that found in acute experiments in the heart-lung preparation. In the latter case the increased metabolic demands of the heart muscle are met by a rise in coronary blood flow or oxygen extraction. In this respect the response of the heart is similar to that of other organs or of the organism as a whole. When, however, the increase in load is prolonged over months or years, the heart meets its increased energy requirements not by a rise in oxygen consumed per unit weight but by an increase in the total weight of its muscle. Thus, in the hypertrophied heart the oxygen consumption per unit weight can be normal, while the total left ventricular oxygen consumption is increased (Fig. 7).

In the six patients with congestive heart failure the oxygen consumption per unit of left ventricular tissue is slightly elevated (Table II and Fig. 5). Four of these had mitral stenosis with some clinical evidence of regurgitation. Two had arteriosclerotic heart disease. The left ventricle in all these patients showed radiologic evidence of enlargement, which was particularly marked in one patient with arteriosclerotic heart disease. Starling[20] has shown that acute failure of the heart in vitro was accompanied by a significant increase in the oxygen consumption and a decrease in cardiac output. Since the oxygen consumption per unit weight is not increased in these patients, the diastolic fibers must either remain constant or Starling's concept is not valid. Investigations are now in progress to elucidate this problem further.

The cardiac efficiency of normal left ventricular muscle averages 23 per cent (Table II). This value is considerably higher than that obtained in the heart-lung preparation. The difference is probably the result of the relatively low cardiac output of the isolated dog's heart. When, however, the cardiac output of the dog's heart in vitro is raised to levels comparable to those observed in the normal human heart, the left ventricular efficiency approaches that seen in normal man.[14] An estimation of left ventricular efficiency in hearts with cardiac hypertrophy is impossible for reasons outlined above. When, however, an efficiency, calculated on the basis of normal heart weight, is low, it is significant. This is the case in the six patients with congestive heart failure. Table II shows that the left ventricular efficiency ranges from 10 to 17 per cent. A similar decrease in cardiac efficiency was found by Starling and Visscher[20] in the failing heart in vitro. This was the result of decreased cardiac work and of increased cardiac oxygen consumption. Moe and Visscher[7] in later studies were able to obtain lowered cardiac efficiency in failure by decrease

in cardiac output alone. In these experiments the oxygen consumption of the heart remained constant, since the diastolic volume of the heart was maintained. The assumption may be ventured, therefore, that in certain types of human heart failure, the cardiac efficiency is low.

SUMMARY

The left ventricular coronary blood flow and left ventricular oxygen consumption per unit weight have been determined in twenty-six patients by means of the nitrous oxide method in conjunction with catheterization of the coronary sinus. The studies were performed on normal individuals and on patients with various forms of cardiovascular disease.

The technique of coronary sinus catheterization and of the nitrous oxide method as applied to the coronary circulation in man have been presented.

In the normal subject the left ventricular coronary blood flow per 100 grams per minute and the left ventricular oxygen consumption per 100 grams per minute averaged 65 c.c. and 7.8 c.c., respectively. The average oxygen extraction was 12 volumes per cent.

In acutely anemic patients the left ventricular coronary blood flow per 100 grams per minute was slightly increased, whereas the left ventricular oxygen consumption per 100 grams per minute and the left ventricular oxygen extraction were reduced.

In patients with essential hypertension, left ventricular coronary blood flow per 100 grams per minute, left ventricular oxygen consumption per 100 grams per minute, and left ventricular oxygen extraction were normal.

In patients with coarctation of the aorta, the average left ventricular coronary blood flow per 100 grams per minute, left ventricular oxygen consumption per 100 grams per minute, and left ventricular oxygen extraction were all increased.

In congestive failure due to mitral stenosis and insufficiency and to arteriosclerotic heart disease the left ventricular coronary blood flow per 100 grams per minute, was normal. The oxygen extraction was slightly elevated. Despite clinical and radiological evidence of marked left ventricular enlargement, the oxygen consumption per 100 grams per minute was only slightly elevated.

Left ventricular coronary blood flows per 100 grams per minute were increased in patients with aortic insufficiency, arteriovenous fistula, and hyperthyroidism. The left ventricular coronary blood flow was normal in the patient with aortic stenosis. The left ventricular oxygen consumption per 100 grams per minute was normal in patients with aortic stenosis, with arteriovenous fistula, and with hyperthyroidism. It was elevated in the patient with aortic insufficiency.

In one patient with clinical and electrocardiographic evidence of coronary occlusion with myocardial damage, the left ventricular coronary flow per 100 grams per minute, the oxygen extraction, and the left ventricular oxygen consumption per 100 grams per minute were markedly reduced.

The results indicate that chronic increase in the energy requirements of the heart were met, not by an increase in the oxygen consumption per unit weight, but by an increase in the total oxygen consumption due to hypertrophy.

The efficiency of the failing heart was low as a result of markedly decreased work in conjunction with slightly increased oxygen consumption.

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THE ROLE OF DESICCATED THYROID AND POTASSIUM IODIDE IN THE CHOLESTEROL-INDUCED ATHEROSCLEROSIS OF THE CHICKEN

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EVER since Anitschkow[1] first succeeded in producing experimental arteriosclerosis in the rabbit, numerous attempts have been made to find some means of preventing or inhibiting the development of the cholesterol-induced lesions, or of causing the regression of the formed lesions. To date, the most encouraging progress in this direction has been with the use of the organic and inorganic iodides and of whole thyroid preparations. The voluminous and contradictory literature on the subject has recently been reviewed by Hueper.[11] There has been some hesitancy on the part of many observers to accept this work, all of which has been done in the rabbit, on the grounds that this animal is not a suitable experimental animal for work in arteriosclerosis. Their arguments have been summarized by Duff.[10] In a search for a more suitable animal, Dauber and Katz[12] found that arteriosclerosis could be produced in the chicken by the feeding of a high-cholesterol diet. The atherosclerosis was characterized by intimal changes which resembled those seen in man. Furthermore, the chicken, unlike the rabbit, is an omnivore, and normally ingests considerable amounts of cholesterol in its diet. Perhaps of even greater importance is the fact that the chicken normally develops arteriosclerosis after the age of six months, and that by the age of one and one-half years more than 50 per cent of chickens show some evidence of this spontaneous type of arteriosclerosis.[13] Because of the manifest advantages of this animal for studies of experimental atherosclerosis, we decided to employ it in our reinvestigation of the role of desiccated thyroid and potassium iodide in experimental cholesterol-induced atherosclerosis.

METHODS

Three separate series of experiments were run; the first between March and July, 1946 (Series one), the second between August and November, 1946 (Series two), and the third between August and November, 1947 (Series three). White Leghorn chicks between the ages of 5 and 7 weeks were used throughout.

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TABLE I. COMPOSITION OF THE EXPERIMENTAL GROUPS AND DIETS IN THE THREE SERIES

SERIES	SUBGROUP	NO. OF CHICKENS IN SUBGROUP	BASAL DIET	CHOLESTEROL ADDED (PER CENT)	DESICCATED THYROID	POTASSIUM IODIDE
One	Cholesterol controls	16	Chick starter mash	2	—	—
	Thyroid-Cholesterol	16	Chick starter mash	2	200 mg./kg./day	—
	Potassium iodide-Cholesterol	16	Chick starter mash	2	—	800 mg./kg./day
Two	Cholesterol controls	10	Chick starter mash	1	—	—
	Thyroid-Cholesterol	8	Chick starter mash	1	1.0 Gm./kg./day	—
	Potassium iodide-Cholesterol	10	Chick starter mash	1	—	2.0 Gm./kg./day
Three	Normal controls	10	Chick starter mash	—	—	—
	Cholesterol controls	10	Chick starter mash	1	—	—
	Cholesterol controls	10	Chick starter mash	0.5	—	—
	Thyroid-Cholesterol	20	Chick starter mash	1	700-800 mg./kg./day	—
	Thyroid-Cholesterol	20	Chick starter mash	0.5	700-800 mg./kg./day	—
	Potassium iodide-Cholesterol	20	Chick starter mash	1	—	1.4-1.5 Gm./kg./day
	Potassium iodide-Cholesterol	20	Chick starter mash	0.5	—	1.4-1.5 Gm./kg./day

Male and female chicks were used in equal proportions in the first two series, and male chicks only were used in Series three. The compositions of the diets and the number of chickens in each group are shown in Table I. The base of the diet was chick starter mash obtained from commercial sources. Cholesterol was suspended in 20 per cent cottonseed oil and thoroughly mixed with the mash. In Series one and two, potassium iodide was dissolved in water and given two to three times a week by pipette, and in these two series desiccated thyroid was given in tablet form by mouth. In Series three, both the potassium iodide and the desiccated thyroid were mixed with the mash. The dosages of cholesterol employed were 2 per cent in Series one, 1 per cent in Series two, and 0.5 and 1 per cent in Series three. The dosages of desiccated thyroid were 200 mg. per kilogram per day in Series one, 1 Gm. per kilogram per day in Series two, and 700 to 800 mg. per kilogram per day in Series three. The dosages of potassium iodide were 800 mg. per kilogram per day in Series one and 2 Gm. per kilogram per day in Series two. In Series three, the dose was 1.4 to 1.5 Gm. per kilogram per day of potassium iodide.

Autopsies were performed on all animals, and careful gross and microscopic examinations were made. The heart and aorta of each animal were dissected out en bloc and carefully examined for atheromatous lesions. The lesions were fully described and sketched on prepared forms. They were graded for severity on an arbitrary scale of values from 0 to 4, depending on the severity of the lesions.[19] The thoracic and abdominal portions of the aorta were graded separately, and the results were later combined as the total gross grading. Sections were also taken for microscopic examination. Total blood cholesterols were done at biweekly intervals by the method of Schoenheimer and Sperry.[20]

RESULTS

The results have been tabulated on the basis of the total gross grading for the separate series and subgroups in Table II, and for all subgroups combined in Table III. For purposes of statistical analysis the data were rearranged in Table IV to demonstrate the effects obtained by thyroid and potassium iodide with different cholesterol loads. From this table it is apparent that at all concentrations of cholesterol, the chickens which received desiccated thyroid showed a lesser degree of atherosclerosis than did the control birds, which received only cholesterol. This effect was most marked in the group receiving 1 per cent cholesterol and thyroid (Series two), and least marked in the group receiving 2 per cent cholesterol and thyroid (Series one). The combined results for all the thyroid groups gave a chi square of 9.7, a value which is statistically significant. Reference to Table IV indicates that the results obtained with potassium iodide were equivocal. With cholesterol concentrations of 0.5 per cent and 2 per cent, the simultaneous feeding of potassium iodide appears, statistically, to aggravate the lesions. This did not hold true for the potassium iodide group of Series two, which received the highest dosage of the drug given and in which group the potassium iodide appeared, statistically, to have some effect in reducing the severity of the vascular lesions.

TABLE II. TOTAL GROSS GRADING OF ATHEROSCLEROTIC LESIONS OF THE AORTA IN INDIVIDUAL GROUPS (NUMBER IN EACH GROUP)

SERIES	GROUP	GRADE 0-1	GRADE 1½-3	GRADE 3½-8
One	2% Cholesterol controls	3	7	5
	2% Cholesterol-Potassium iodide	1	7	6
	2% Cholesterol-Thyroid	3	8	5
Two	1% Cholesterol controls	2	4	4
	1% Cholesterol-Potassium iodide	3	5	1
	1% Cholesterol-Thyroid	4	4	0
Three	Normal controls	10	0	0
	0.5% Cholesterol controls	7	3	0
	1% Cholesterol controls	3	6	0
	0.5% Cholesterol-Potassium iodide	6	10	4
	1% Cholesterol-Potassium iodide	8	5	2
	0.5% Cholesterol-Thyroid	10	1	0
	1% Cholesterol-Thyroid	4	5	0

Method of grading is that described previously[19]; since thoracic and abdominal lesions are added together the grades run from 0 to 8.

TABLE III. COMBINED GROSS GRADING OF ATHEROSCLEROTIC LESIONS OF THE AORTA IN ALL SERIES

GROUP	NUMBER WITH GRADE 0-1	PER CENT OF TOTAL IN GROUP	NUMBER WITH GRADE 1½-3	PER CENT OF TOTAL IN GROUP	NUMBER WITH GRADE 3½-8	PER CENT OF TOTAL IN GROUP
Cholesterol controls (0.5-1-2%)	15	33	20	45	9	22
Cholesterol-Thyroid	21	48	18	41	5	11
Cholesterol-Potassium iodide	18	31	27	47	13	22

Blood Cholesterol Levels.—The results for Series three are shown in Fig. 1,*A* and *B*, and are representative of those obtained in the two preceding series. In this series both the birds fed only 0.5 per cent and those fed 1 per cent cholesterol showed rapid and steady rises to high blood cholesterol levels. The groups which received potassium iodide and cholesterol showed blood cholesterol levels which were closely parallel to, but exceeded the levels for the birds fed cholesterol alone. The blood cholesterol values in the groups receiving thyroid and cholesterol were consistently about 50 per cent of those in the groups receiving cholesterol alone.

DISCUSSION

Liebig[2] demonstrated clearly that iodides would prevent the development of arteriosclerotic lesions in rabbits which were simultaneously receiving a high-cholesterol diet. This pioneer work has since been confirmed in the rabbit by many investigators. In 1927, Shapiro[3] reported that thyroidectomized rabbits fed lanolin in cottonseed oil, in addition to their regular diet, were abnormally susceptible to the development of atherosclerotic lesions. Subsequent

TABLE IV. COMBINED GRADING OF ALL GROUPS ARRANGED ACCORDING TO CHOLESTEROL CONTENT OF DIET

	NUMBER WITH GRADE 0-1	NUMBER WITH GRADE 1½-8	PER CENT OF BIRDS WITH GRADING >1	CHI²*	PROBABILITY† (PER CENT)
Cholesterol 0.5%					
Control	7	3	30		
Thyroid	10	1	9	0.44	
Cholesterol 1%					
Control	5	14	73		
Thyroid	14	5	26	8.5	<5
Cholesterol 2%					
Control	3	12	80		
Thyroid	3	5	63	0.83	
Total of three series				9.7	<5
Cholesterol 0.5%					
Control	7	3	30		
Potassium iodide	6	14	70	3.82	5
Cholesterol 1%					
Control	5	14	73		
Potassium iodide	11	13	54		
Cholesterol 2%					
Control	3	12	80		
Potassium iodide	1	13	93	0.22	

*Chi² test of independence statistically.

†When P is less than 5 per cent, the difference is considered to be statistically significant.

reports from other investigators, namely, Turner and his associates,[4,5,6] to the effect that desiccated thyroid would prevent the development of atherosclerosis and hypercholesterolemia, suggested that the thyroid gland might play a very important role in the pathogenesis of experimentally induced atherosclerosis in the rabbit. The nature of this role has been elucidated in large part through the studies of Turner and his associates. They showed that in the rabbit the thyroid exercises at all times a restraining influence on the blood cholesterol, strong enough to overcome the effect of the feeding of large amounts of cholesterol by mouth.[5] The removal of the thyroid gland resulted in rising blood cholesterol levels in normal animals and in those receiving cholesterol either with high or normal blood cholesterol levels at the start, the last being the so-called "resistant" rabbits.[5] They also discovered that the protective action of potassium iodide depended on the presence of the thyroid gland; and that potassium iodide failed to affect the blood cholesterol levels of the rabbit in the absence of the thyroid gland.[7]

Thyroid hormone, desiccated thyroid, and potassium iodide have all been shown to have striking effects on the levels of cholesterol in the blood.

Thyroid hormone and desiccated thyroid will prevent the blood cholesterol from rising to the high levels seen in cholesterol-fed animals, and will continue to exert this effect in the face of continued feeding of a high-cholesterol diet for many weeks.[4,5] Potassium iodide will act only in the presence of the thyroid, as was demonstrated by Turner and Khayat,[7] and then its effect in restraining the rise in blood cholesterol is only temporary.

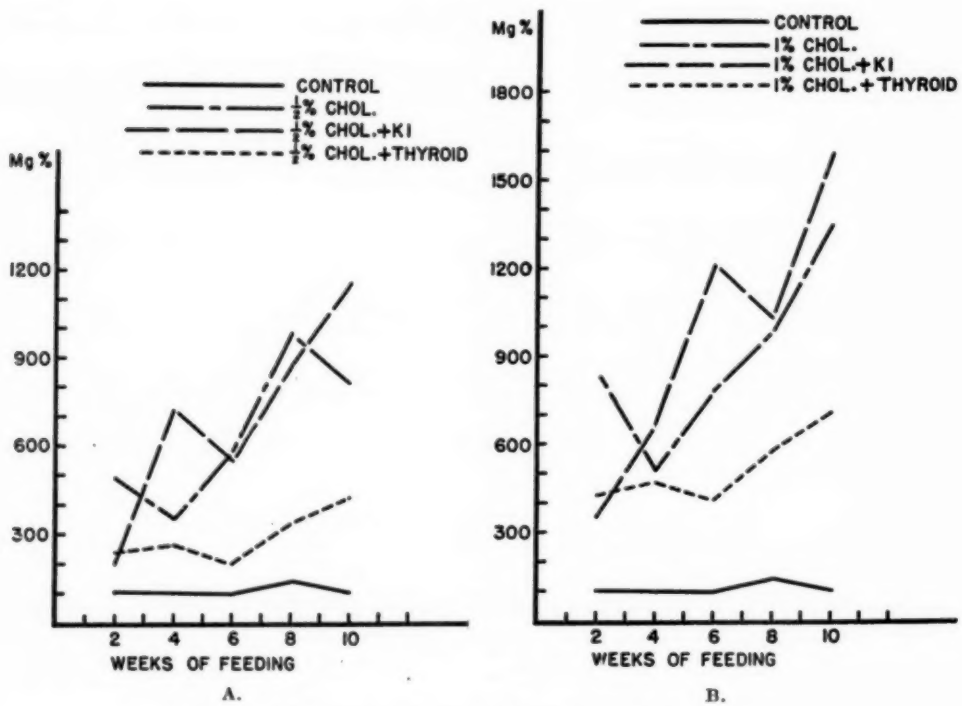

Fig. 1.—*A* and *B*, Blood cholesterol levels (total) Series three.

From these statements, it would appear that the effect of thyroid gland extracts in preventing arteriosclerosis is most likely through the action of these substances in restraining the blood lipids from rising to the high values seen in the control cholesterol-fed animals.

The picture, however, is not so simple as it seems. Although in most published reports there seems to be a close coincidence between the occurrence of atherosclerotic lesions and the levels of blood cholesterol, there are a number of reports which indicate that the protective action of potassium iodide and other iodides may not be entirely due to their effect on the blood cholesterol via the thyroid gland. Page and Bernhard[8] found that the di-iodide of ricinsterolic acid, when administered to rabbits simultaneously receiving a high-cholesterol diet, had no effect on the hypercholesterolemia and lipemia, although it exerted a protective effect on the vascular tissue. Ungar[9] observed

the protective action of organic iodides in thyroidectomized animals, and Turner and Bidwell[6] confirmed the protective action of potassium iodide on the thyroidectomized rabbit.

The mechanism of the protective effect of potassium iodide is not understood at present. It is known that iodides will combine in vitro with protein to form a biologically active substance which resembles thyroid hormone.[16] It is also known that the function of the thyroid gland is (a) to selectively accumulate inorganic iodides and (b) to release elementary iodine for the formation of thyroid hormone.[17] If free iodine is fed to a thyroidectomized animal, it can be utilized peripherally.[18] There is proof that free iodine acts peripherally by forming a thyroid-hormonelike substance through combination with body proteins in areas other than the specialized tissues of the thyroid gland.[18] The differences in the results obtained by various investigators are probably due to the presence or absence of free iodine in the iodide employed. In thyroidectomized animals, free iodine would act peripherally, while potassium iodide or other combined iodine would be ineffective.

Our results demonstrate clearly that when potassium iodide is given dissolved in water, with no free iodine present, it has no clear-cut protective effect on the degree of the atherosclerosis induced by simultaneous cholesterol feeding. With the lower dosage level of potassium iodide there even appears to be an aggravation of the severity of the cholesterol-induced lesions. It would appear, therefore, that the ability of the thyroid gland of the chick to produce thyroxin is not increased by its being presented with an abundance of inorganic iodide. Indeed, it would appear that under these conditions the ability of the thyroid to produce its hormone is impaired.

Our results confirm those of Turner and his associates,[4] who found that desiccated thyroid substance, when fed in large doses together with cholesterol, is protective to a considerable extent against the development of atherosclerosis in the rabbit. We have observed only a partial and statistical degree of protection, which depended in large part on the relative doses of cholesterol and thyroid administered. This is in contrast to the almost complete protection observed by Turner and others[4] in the rabbit. Again, in contradiction of Turner,[4] we have been unable to observe any protective action of potassium iodide in the chicken. The recent work of Dvoskin,[18] which showed the ability of the peripheral tissues to utilize free iodine for the formation of thyroxin-like material, would suggest that the role of iodine must be re-evaluated, both in the rabbit and in the chicken, by this newer method.

The behavior of the blood cholesterol under the conditions imposed was identical with that reported by Turner[4,6] as far as the effect of thyroid was concerned. Whereas Turner observed a temporary effect of potassium iodide in restraining the blood cholesterol rise due to the feeding of cholesterol, no such phenomenon was observed in our series. Instead, the potassium iodide caused a rise of the blood cholesterol values above normal, and this effect was maintained throughout the course of the experiment. At present, it is not possible to say whether the effect of thyroid substance in protecting the vascular tissues

against the development of atherosclerosis is due simply to its action in inhibiting the rise in blood cholesterol which occurs when cholesterol is fed, or whether thyroid substance also possesses some specific effect on the vascular tissues. The work of Fleischmann and Shumacker[14] indicates that thyroxin causes a shift of cholesterol from the blood to the tissues without affecting the total amount of cholesterol in the body. Hueper[11] has suggested that the instability of the lipid-protein complex in the blood leads to the deposition of lipids in the arterial intima, and that the protective action of thyroid hormone lies in "stabilizing" the lipid-protein complex of the blood.

Finally, the amount of desiccated thyroid given was very large, in the neighborhood of 0.8 to 1.0 Gm. per kilogram per day, which represents the upper limit of tolerance of the chicken for this drug. Herrmann[15] and others have used desiccated thyroid and potassium iodide in clinical trials and reported some effect. It is difficult to evaluate the effect of the drugs in clinical material, and it would seem by inference from the animal work that the doses of thyroid required would be unsafe for clinical use.

SUMMARY

1. Chickens were fed desiccated thyroid and potassium iodide, together with cholesterol, in varying concentrations, in an attempt to determine the effect, if any, of these substances on cholesterol-induced atherosclerosis.

2. Potassium iodide in doses ranging from 800 mg. per kilogram per day to 2,000 mg. per kilogram per day gave equivocal results. With a dose of 2,000 mg. per kilogram per day in animals receiving 1 per cent cholesterol, some protective action was observed. In chickens receiving 0.5, 1, and 2 per cent cholesterol and smaller doses of potassium iodide, the drug appeared to aggravate the severity of the lesions.

3. Desiccated thyroid in doses of from 200 mg. per kilogram per day to 1,000 mg. per kilogram per day gave consistent results. Some degree of protection was seen in all series. The degree of protection depended on the relative doses of thyroid and cholesterol given.

4. Desiccated thyroid minimized the rise in the blood cholesterol levels seen in the cholesterol-fed control chickens. This inhibitor effect of desiccated thyroid on the blood cholesterol was maintained throughout the course of the experiment. In potassium iodide-treated chickens the blood cholesterol levels were higher than in the cholesterol-fed control chickens.

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PRODUCTION OF ARTERIOSCLEROSIS IN DOGS BY CHOLESTEROL AND THIOURACIL FEEDING

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PROGRESS in the study of arteriosclerosis is largely dependent on the reproduction of the disease in animals because this pathologic condition cannot be adequately diagnosed and followed clinically. Until recently, the experimental arterial lesions that most closely resembled human arteriosclerosis occurred in rabbits, following an elevation of blood cholesterol as a result of a high-cholesterol diet.[1] Numerous attempts[2,3,4] to produce arteriosclerosis in other species have been unsuccessful except in the chicken.[5] Although the arteriosclerosis in rabbits is similar in many respects to that which occurs in man, Duff[3] and other investigators[7] have emphasized three important objections: (1) The distribution of the lesions in rabbits differs from that occurring in man in that the lesions are most extensive in the abdominal aorta and its branches. In addition, cerebral and renal arteriosclerosis does not occur in rabbits. (2) The morphologic appearance of the lesions in rabbits resembles that seen in the early stages of arteriosclerosis in man, but the more advanced type of lesion does not develop. (3) The feeding of cholesterol fails to result in a significant hypercholesterolemia and arterial lesions in omnivorous mammals, such as the dog, rat, cat, or monkey, whose diet normally contains cholesterol.

However, in a recent study from this laboratory,[8] it was demonstrated that arterial lesions in dogs, similar in distribution and microscopic appearance to human arteriosclerosis, resulted from prolonged hypercholesterolemia.

The present communication records further studies confirming and extending the original report.

METHOD

Seven mongrel dogs, 3½ months old at the onset of the experiment, were used. After an initial control period of one to two weeks, the animals were divided into three groups. Group A, consisting of three animals (No. 428, No. 429, and No. 430), was fed 1.0 Gm. of thiouracil* daily together with the regular diet

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*Thiouracil was kindly supplied for this investigation by Dr. S. M. Hardy of Lederle Laboratories.

(Spratt's meat fibrine dog cakes) for fourteen to fifteen months. Group B, consisting of two dogs (No. 2951 and No. 2947), was fed 10 Gm. of crystalline cholesterol daily together with the regular dog food for sixteen months. The cholesterol was dissolved in ether, mixed through the dog food, and the ether then allowed to evaporate. Group C, consisting of two dogs (No. 2935 and No. 2934), were fed increasing amounts of thiouracil daily, 0.8 Gm., for the first two months, 1.0 Gm. for the third month, and 1.2 Gm. from the fourth through the twelfth month, plus 10 Gm. of cholesterol added to the regular diet. Serum cholesterol determinations, using the method of Schoenheimer and Sperry,[9] were made biweekly during the course of the study. All of the animals remained in good general health and gained weight during the experiment.

The animals were sacrificed at the end of the study by exsanguination under phenobarbital sodium anesthesia. Post-mortem examinations were made in each instance.

TABLE I. SERUM CHOLESTEROL VALUES IN DOGS (MG. PER 100 CUBIC CENTIMETERS)

Group A

DOG NUMBER	CONTROL PERIOD			THIOURACIL PERIOD		
	RANGE	AVERAGE	MONTHS	RANGE	AVERAGE	MONTHS
428		225	1	309–530	408	14
429		322	1	307–594	415	15
430		131	1	176–490	359	14

Group B

DOG NUMBER	CONTROL PERIOD			CHOLESTEROL PERIOD		
	RANGE	AVERAGE	MONTHS	RANGE	AVERAGE	MONTHS
2947	178–180	179	2	294–736	449	16
2951	111–150	130	2	212–624	408	16

Group C

DOG NUMBER	CONTROL PERIOD			CHOLESTEROL PERIOD			CHOLESTEROL AND THIOURACIL PERIOD		
	RANGE	AVERAGE	MONTHS	RANGE	AVERAGE	MONTHS	RANGE	AVERAGE	MONTHS
2935	144-147	145	2	400-565	447	1	505–2350	1206	12
2934	79-178	128	2	344-418	388	1	570–1617	1089	12

RESULTS

Serum Cholesterol Determinations.—The serum cholesterol levels of the three animals in Group A on thiouracil alone averaged 408 mg. per cent, 415 mg. per cent, and 359 mg. per cent, respectively, during the thiouracil period of fourteen to fifteen months (Table I).

The serum cholesterol levels of the two dogs on the high-cholesterol program (Group B) for sixteen months averaged 449 and 408 mg. per cent, respectively, during the course of the feeding. This represented an average increase of 270 and 278 mg. per cent, respectively, over the control values (Fig. 1).

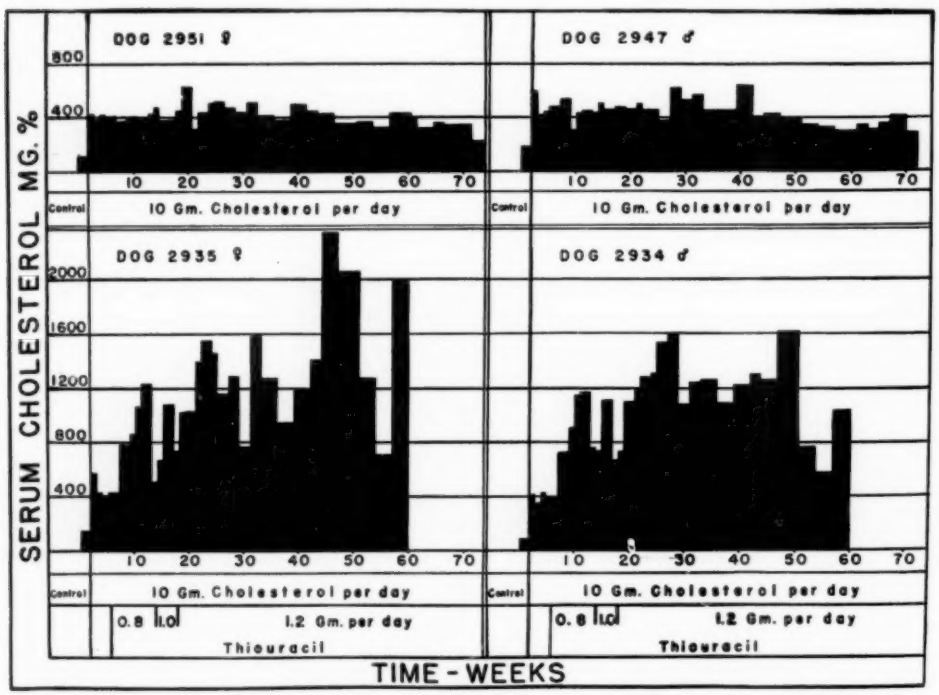

Fig. 1.—Levels of total serum cholesterol, as determined at weekly intervals during preliminary control period and during periods of cholesterol feeding in Dogs 2951 and 2947, and during cholesterol plus thiouracil feeding in Dogs 2935 and 2934.

The dogs on the high-cholesterol diet and thiouracil (Group C) had average serum cholesterol levels of 1,206 and 1,089 mg. per cent, respectively, during the twelve months of the experiment. This represented an average increase of 1,061 mg. and 961 mg., respectively, over control levels (Fig. 1).

Arterial Lesions.—A complete necropsy was performed on all animals immediately after sacrifice. All organs as well as the aorta and its major branches were examined microscopically. The three dogs on thiouracil for fourteen to fifteen months were completely free of arterial lesions.

One of the two dogs on the high-cholesterol diet had a few fine, raised, yellow streaks in the abdominal aorta. On microscopic section, these were seen to consist of lipid depositions in the aortic intima, forming an early arteriosclerotic lesion. The second dog on the high-cholesterol diet had no arterial lesions.

Fig. 2.—Abdominal aorta showing multiple intimal arteriosclerotic plaques which coalesce about exit of branches. The circular muscle bundles of the iliac arteries are accentuated by the plaques.

Post-mortem examination of the two dogs on the cholesterol plus thiouracil regime revealed extensive generalized arteriosclerosis. The lesions varied in size from small, pin-point, yellowish elevations of the intima to large coalescing plaques. The lesions were most marked in the abdominal aorta and its branches. The coronary arteries were diffusely involved, with resulting narrowing of the lumen of the vessels. Gross lesions were present on the anterior leaflet of the mitral valve as well as in the sinuses of Valsalva. The arteries forming the circle

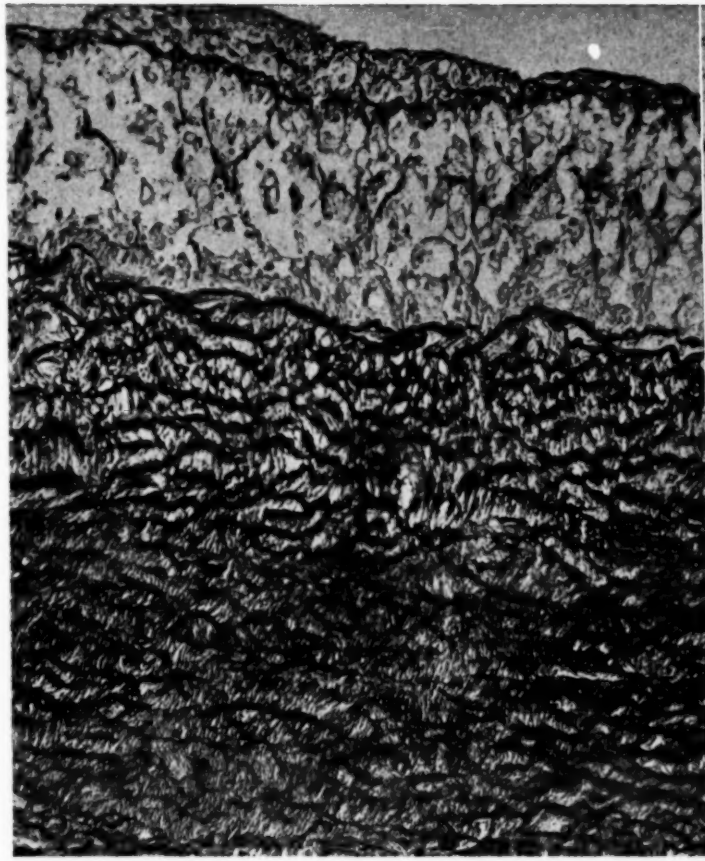

Fig. 3.

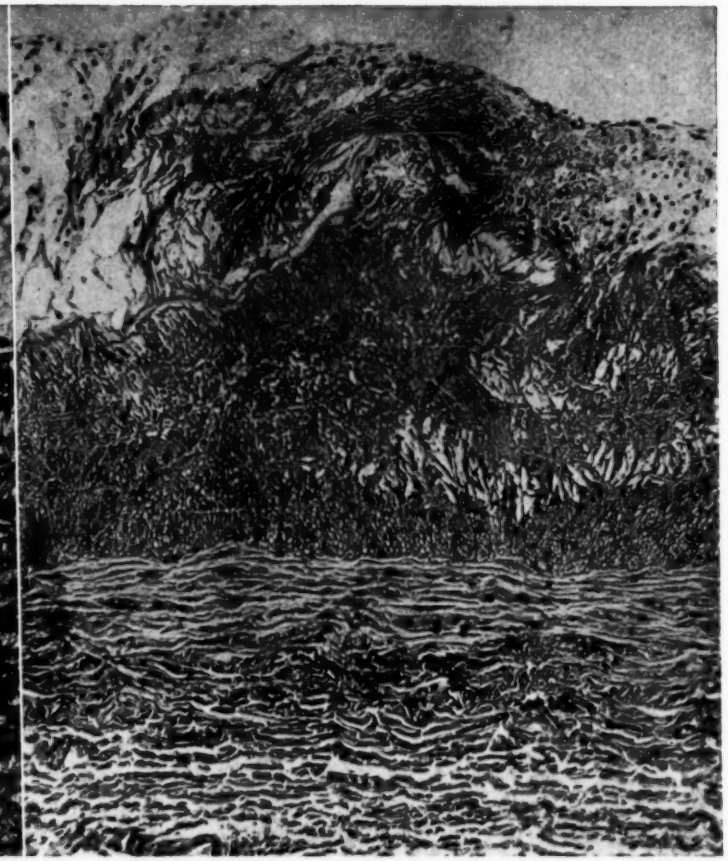

Fig. 4.

Fig. 3.—Thoracic aorta. An early arteriosclerotic lesion showing a thickening of the intima by lipid infiltration with the internal elastica intact. Lipid has also infiltrated to the media, giving it a loose vacuolated appearance. Elastic tissue stain ×163.

Fig. 4.—Iliac artery. An advanced arteriosclerotic plaque with foam cells and fibrosis. Vacuolated spaces representing lipid appear in the media. The internal elastica is visible at the left but disappears beneath the fibrotic area of the plaque. Hematoxylin and eosin stain, ×163.

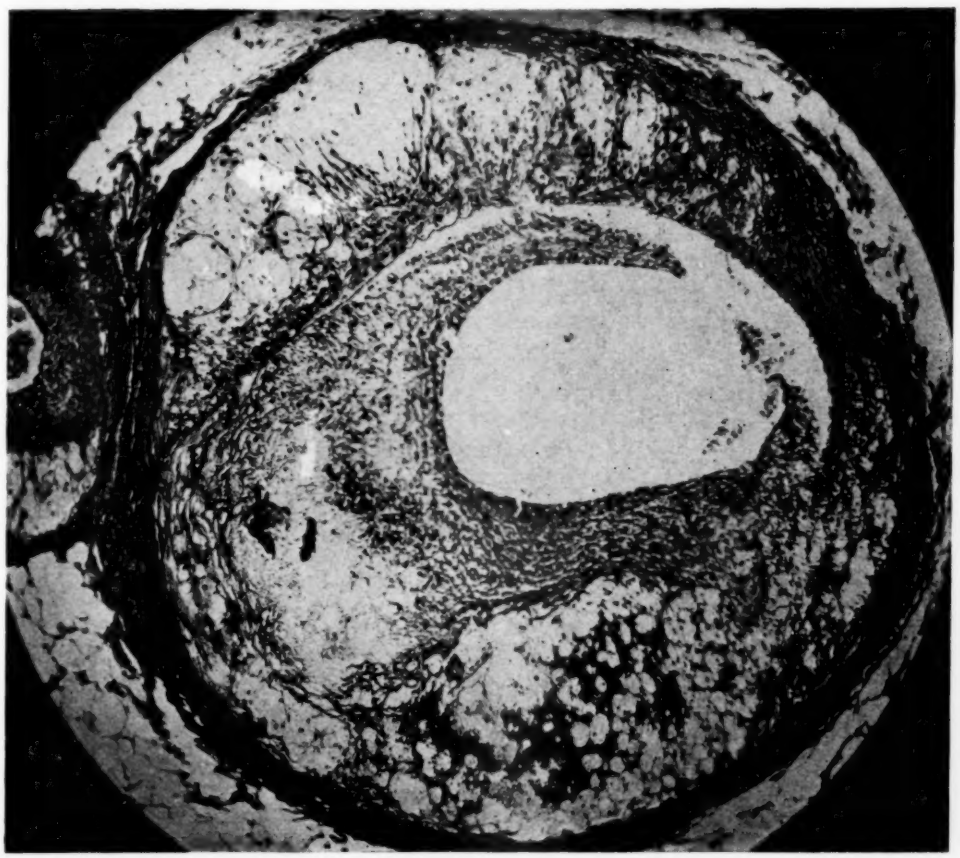

Fig. 5.—Coronary artery showing advanced arteriosclerosis with many of the sequelae of human arteriosclerosis. The lumen is narrowed by diffuse atheromatous deposits. Within the plaque are hemorrhage, hyalinization, and calcium. The media has been partially replaced by lipid deposits. Hematoxylin and eosin stain, ×86.

of Willis contained numerous yellow atheromatous plaques. In addition, gross plaques were present in the thoracic aorta, thyroid, subclavian, innominate, iliac, femoral, mesenteric, and renal arteries.

Microscopic examination of the lesions described (Figs. 2-6) showed all stages of development seen in human arteriosclerotic plaques. Infiltration of the intima with foam cells and proliferation of the intima were present in the early stages. In older lesions, a layer of fibrous tissue, which was partially hyalinized, covered and depressed the lipid-containing foam cells deep into the plaque. Hemorrhage and calcification occurred within the plaques of the coronary arteries. Varying amounts of lipid could be demonstrated within the media of the arteries beneath the intimal plaques.

The only other findings of note were the hyperplasia of the thyroid gland and the presence of large amounts of fat in the liver, spleen, and kidneys comparable to that described in the original experiment.[8]

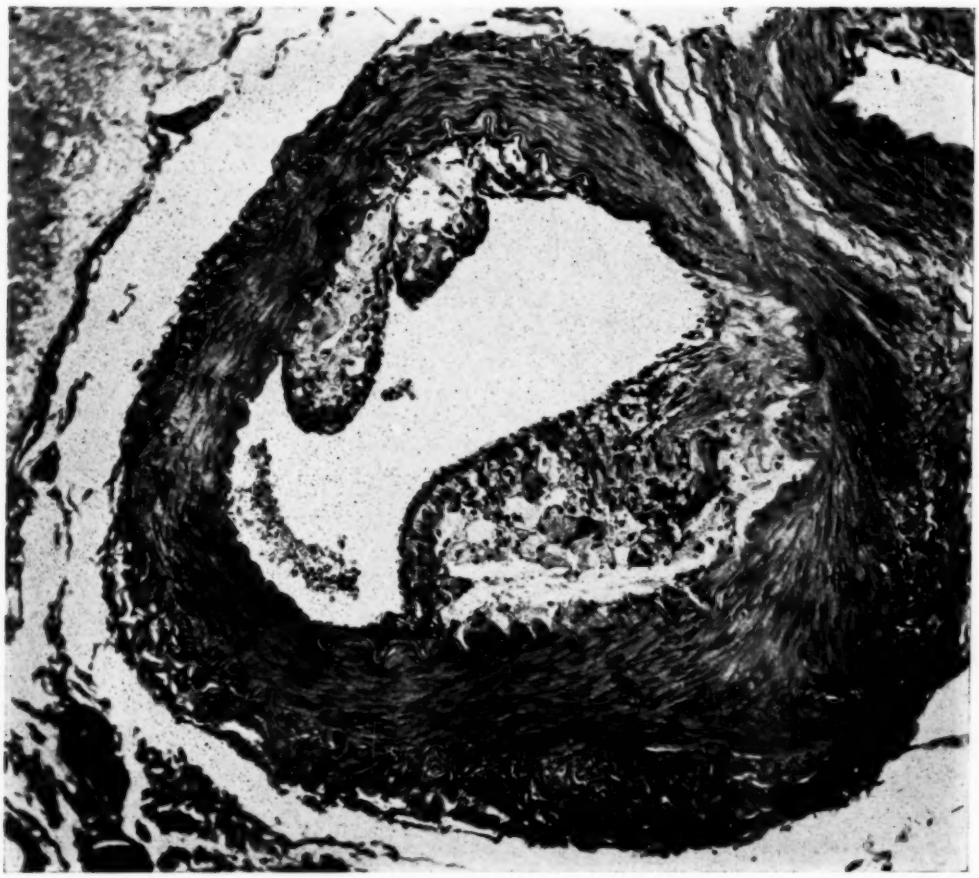

Fig. 6.—Middle cerebral artery. Initimal atheromatous deposits narrow the lumen. Fibrous tissue beneath the endothelium and at the edges of the larger plaque is encroaching upon the foam cells. Hematoxylin and eosin, ×144.

DISCUSSION

The present report confirms and extends a previous study from this laboratory in that extensive and generalized arteriosclerosis has been produced in young dogs by the feeding of cholesterol and thiouracil for one year. In addition, the feeding of cholesterol for sixteen months without thiouracil has been shown to result in the production of early arteriosclerotic plaques in the abdominal aorta of one of the two young dogs. The feeding of thiouracil without cholesterol to three animals for fifteen months failed to cause arterial lesions.

The present study differs from the earlier one in two respects: First, the animals in this experiment were 3½ months old at the onset while the exact ages of the animals in the initial report were not known. Second, in the previous study, the cholesterol was suspended in 40 c.c. of cottonseed oil and then mixed through the dog food, whereas in the present experiment, no added fat was

used; the cholesterol was dissolved in ether and mixed through the dog food, and the ether was then allowed to evaporate.

The degree and extent of arteriosclerosis in the dogs that have been studied to date bears a direct relationship to the duration and elevation of the serum cholesterol. The average cholesterol level must exceed 450 mg. for more than one year before arteriosclerotic lesions are evident. It might be possible to produce arteriosclerosis in a shorter period of time if higher serum cholesterol levels are maintained.

In addition to the production of arteriosclerosis of the aorta and its branches, cerebral arteriosclerosis has occurred in the animals on the high-cholesterol and thiouracil program. Previous attempts to produce experimental arteriosclerosis of cerebral vessels have been unsuccessful, even in the rabbit.[10] This difference between experimental arteriosclerosis and human arteriosclerosis has formerly been cited as one of the objections to transferring the results of experimental studies in animals to man. The distribution of the arteriosclerosis in the aorta of the dog is similar to that occurring in man in that the lesions are most marked in the abdominal aorta and its branches while in the rabbit the lesions are most prominent in the ascending aorta and the arch of the aorta. Thus, the experimental arteriosclerosis as produced in the dog is analogous to that in man so far as the site of occurrence of the lesions is concerned.

In the microscopic sections it can be seen that all stages from early to advanced forms of arteriosclerosis occurred in the dogs. The lesions of the coronary arteries, in particular, are almost identical with the human variety in that narrowing of the lumen was produced by thickening of the arteries, fibrosis, calcification, and hemorrhage into the wall of the arteriosclerotic placque. The experimental arteriosclerosis in dogs is comparable to that occurring in man, whereas in the rabbit only the early stages of the arteriosclerotic process are seen microscopically.

The objections that have been raised to bring out the disparity between the experimental arteriosclerosis in the rabbit and that which occurs in man are probably the result of species differences and may not represent a fundamental difference in the pathogenesis of the disease process. Certainly the studies in this report indicate that experimental arteriosclerosis, which closely resembles human arteriosclerosis, can be produced in the dog, an omniverous mammal.

Now that an acceptable laboratory tool is available, methods of preventing or curing arteriosclerosis are under study. Lipotropic substances which have been found to be effective in preventing or curing experimental arteriosclerosis in the rabbit[11,12] are being investigated in the dog.

SUMMARY

1. The production of arteriosclerosis in an omniverous mammal, the dog, by the feeding of cholesterol and thiouracil has been confirmed.

2. The resultant arteriosclerotic lesions in the dog have the same anatomical distribution and sites of predilection as do lesions in man, including the occurrence of cerebral arteriosclerosis.

3. The morphological features of the arteriosclerotic lesions in dogs resemble those of human arteriosclerosis in that infiltration of the intima with foam cells and proliferation of the endothelium of the intima occurs in the early lesions, while extension into the media, hyalinization, hemorrhage, and calcification develop in the more advanced placques.

4. It has been demonstrated that thiouracil in the dosage used does not lead to arterial lesions.

5. The feeding of 10 Gm. of cholesterol daily, in addition to the regular diet, containing less than 5.0 per cent fat, without thiouracil, resulted in a moderate hypercholesterolemia and early arteriosclerosis in one dog.

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SURGICAL TREATMENT OF ANEURYSMS

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THE purpose of this paper is twofold. It is, first, to describe our results in operating 218 times on 177 patients who had arterial or arteriovenous aneurysms, and second, to bring to attention a group of patients who have unrecognized arteriovenous connections we call arterial varices.

The possible control of aneurysms has been a challenge to surgeons from the earliest days and surgical history is replete with the attempts in this direction of the most skillful surgeons in this field. Kocher, Miculicz, John Hunter, Halstead, and more recently Matas, Carrel, Reid, Babcock, Holman, and Elkin compose but a partial list of those who tried to control aneurysms. In general, there are two types of aneurysms: those involving the arterial tree only and those in which both the arteries and veins are connected. Either type may result from congenital or developmental failure, from trauma, or from degeneration of vessels due to disease.

Congenital arterial defects are rare, but arteriovenous aneurysms, other than those due to trauma, are, in the main, of a congenital nature. These connections normally present in fetal life sometimes do not close, and in this category can be placed many of the hemangiomas, the port-wine blemishes, and other vascular anomalies, some of which develop into aneurysms as time goes on. Certain of these congenital arteriovenous aneurysms continue to spread despite all types of therapy and they well may be called the carcinoma of the vascular system. They do not kill by metastasizing as do cancers, but they may destroy by locally spreading, always being ahead of efforts of therapy and eventually causing hemorrhage and death. One hundred fourteen of our patients had this congenital type of lesion.

The most common type of trauma is gunshot or stab wounds as seen during the war, but, with the increasing speed of locomotion, more result from airplane or automobile accidents. Twenty-four aneurysms of this type are here reported.

With the longevity which has followed the progress of medicine, more patients are reaching the age at which certain diseases, still unconquered, so weaken the blood vessel walls that aneurysmal dilatations follow. The span

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of life has increased by one-third in the last one hundred years with twice as many people 65 or older alive today as then. Should this same rate be continued, that figure will be doubled again before the end of the century.[1] While our control of certain diseases has been phenomenal, our handling of complications of old age and disease occurring late in life has not kept pace. One example is arteriosclerosis, which is present in 40 per cent of all persons over 40 years of age,[2] with its complications, one of which is aneurysm, developing as the arterial wall degenerates. We include thirty-nine patients in this category.

The symptoms of aneurysm vary with the type, site, duration, and extent of the lesion, and time will not be taken to describe them or the effect of these lesions on the heart and circulation, since they are well known.

In the arterial aneurysm, with the disintegration of the vessel, the wall, and especially the media, dilates and/or ruptures. The inability of any structure, including bone, to stand against these aneurysms is definite. Occasionally, clot may form in an aneurysm and produce spontaneous closure, but this outcome is the exception. In general arterial aneurysms increase in size until rupture or embolism occurs. In the arteriovenous aneurysms, especially the congenital ones, so many vessels are encountered which are of such immature nature that the operation is frequently like putting a scalpel into a wet sponge. Pressure is required for control and these blood spaces, sometimes lined by only a single endothelial layer of cells, tear readily when a clamp is applied and are ligated with the greatest difficulty.

TREATMENT OF ARTERIAL ANEURYSMS

I. *Excision With End-to-End Anastomosis.*—This procedure is the ideal treatment in arterial aneurysms. This is possible in nearly all small traumatic aneurysms and in some others. A radial aneurysm in a boy of 4 years is an example. Occlusion of the radial artery was followed by blanching and evident loss of circulation in the thumb and first two fingers. End-to-end anastomosis even in a vessel this small was accomplished readily with fine silk by rerouting the vessel and flexing the wrist. The hydrodynamic law that pressure at any point in the vessel wall is inversely proportional to the rate of flow helps in making an anastomosis, since the rate of flow is rapid in arteries and wall pressure is therefore low.

II. *Venous Transplant.*—In these patients in whom the aneurysm results in a large arterial defect and when life of the part depends on the arterial continuity, a vein may be used as a transplant. This may be sutured into place. We have used it on four occasions. The use of a tube lined by a vein as advocated originally by Crile[3] and Landon[4] and lately by Blakemore and Lord,[5] is a continuation of this principle. While this tube may occasionally be life saving, rupture has occurred at the tube end; in our experience suture technique is more satisfactory. Blalock[22] and Murray[23] likewise favor suturing.

III. *Obliteration Operation.*—The Matas operation[17] now has had fifty years of trial and where anastomosis is impossible it is the operation of choice, as it does not destroy the collateral circulation developed around the sac. To

this operation we have added the implant of a large contiguous muscle placed directly in the sac. This supplies a core, obliterates the space, and the sac[7,8] is closed over it. We have had no recurrence in this type of procedure and it now has been performed on twenty-eight patients.

IV. *Occlusion by Proximal Ligation.*—In larger arteriosclerotic aortic aneurysms, hopeless without therapy, efforts to obliterate the aorta by ligation have continued. Biggers,[9] Matas,[10] and Elkin[11] each have reported success. We have obliterated the abdominal aorta for aneurysm by ligation below the renal arteries transperitoneally in five instances. In the first four of these we ligated with two cotton tapes in hour glass fashion to avoid too great pressure at one point. In three of these four, rupture followed in from six to eighteen months, the rupture occurring at the site of the proximal tape. In each, the signs of aneurysm disappeared and at autopsy in two the sac was found to be completely clotted, and in the other, partially thrombosed. The other patient has not ruptured in one year and may be cured. It was apparent that abdominal aneurysm could be cured if the technical difficulty of erosion at the ligation site could be solved. Following the work of Reid,[12] we then made an incision in the aorta between two cotton tapes, the distal one tied, and inserted a piece of fascia, with one end protruding, and then tied the proximal tape. A fascial plug proximal to the cotton tape was then present to take the shock of the obliteration. This patient has now survived nearly one year (Fig. 1).

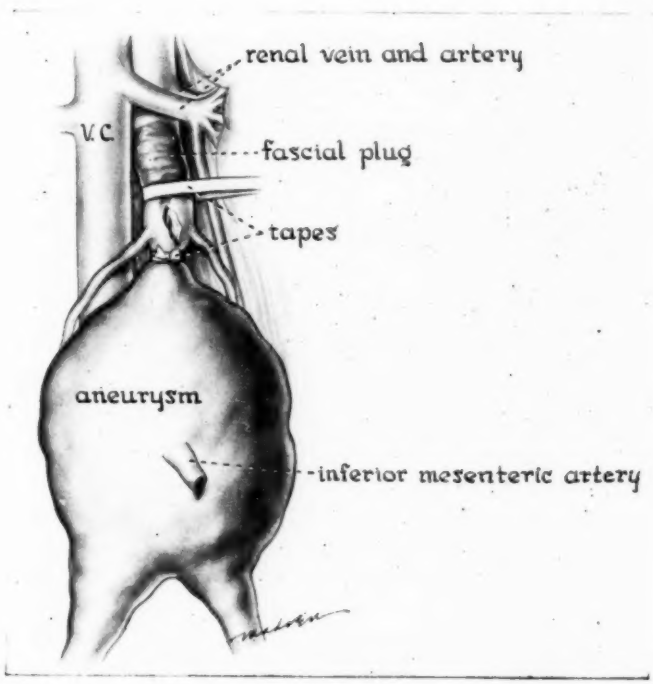

Fig. 1.—Ligation of abdominal aorta for aneurysm after insertion of fascial plug. Fascia placed to to take shock of occlusion from the point of ligation and reduce possibility of rupture.

V. *End-to-End Artery-Vein Anastomoses Distal to Aneurysm* (Babcock[21]).—This operation decreases the wall pressure of the aneurysm by increasing the rate of flow, the blood returning directly to the heart instead of going to the periphery. This method has been used in six thoracic aneurysms and one iliac aneurysm. All but one were done in conjunction with Dr. Babcock.

VI. *Extra-arterial Irritation With Obliteration.*—The fact that an irritant around an aorta will cause sufficient reaction to obliterate it has been known since the work on dogs by Poppe and his associates.[14] Cellophane was used initially and we added talcum powder, another tissue irritant. Experimentally, this produced the ideal slow occlusion, but in diseased vessels the results are not as satisfactory. We have used it six times. One patient whose aneurysm is in the ascending aorta is well after seven years. In another patient with an aneurysm in the innominate artery, operation was followed by a fatal mediastinitis. In one patient with an aneurysm in the aorta at the diaphragm level, operation caused the bruit to disappear for a year. Later, rupture into the thorax occurred and the autopsy showed an arteriovenous aneurysm also present. The possibility of the Cellophane irriatating other vessels must be considered in this case. The other three patients are alive and apparently well.

VII. *Wiring and Coagulation.*—This method, introduced for the treatment of syphilitic aneurysms, is not within the scope of this paper. Blakemore[15] has continued the work of Moore and Corradi[16] and has reported encouraging results. Nearly all surgeons have abandoned this type of treatment. After all operations for arterial aneurysms on an extremity, temporary or permanent sympathectomy is advocated.

Comment.—One patient had a grapefruit-sized false arterial aneurysm of the left subclavian artery, extending from the aorta to the axilla. In operating on this patient control proximal to the aneurysm was difficult to obtain. When a tape was passed around the subclavian artery at its origin, the mass, as a result of its degeneration, broke from the aorta. Hemorrhage which can only be described as "terrific" occurred. Such a hemorrhage from the aorta will exsanguinate a patient within five seconds. The operator's hand was placed immediately in the opening and, with his fingers directly in the aorta, the external bleeding was temporarily controlled. The aneurysmal sac then was openly incised, all clots were evacuated, and the laminated layers removed until the point of rupture of the subclavian aneurysm was revealed. The entire pectoralis major muscle was then mobilized, divided at its insertion on the humerus, and then placed in the opening as the fingers were withdrawn. Efforts were made to place the muscle against but not into the aorta. Two leg rolls, covered with oxidized cellulose were then packed around the area. The muscle was held in place by suturing of the subcutaneous and cutaneous structures over it and the hemorrhage was controlled. Considering this but a temporary expedient, the patient was reoperated one week later and when the wound had been opened it was found that the muscle was well adherent to the aorta, there was granulation about it, and no hemorrhage occurred when the packing was removed. The sac was then obliterated. This case is mentioned because of the

tendency in such an emergency to consider hemorrhage uncontrollable. It emphasized again that pressure in such events is the best method to control bleeding as clamping would have caused further laceration of the vessel. It emphasized also that the best instruments so far devised for the emergency control of hemorrhage are the operator's hands. This patient was alive one year after this emergency.

TREATMENT OF ARTERIOVENOUS ANEURYSM

I. *Excision and End-to-End Anastomoses.*—In small aneurysms of this type this procedure is preferred, especially in end arteries.

II. *Repair of Artery.*—This may be done through the vein wall or through the sac (Fig. 2). Results of this type of operation have been reported by Matas,[17] Elkin,[18] Freeman,[19] and others. We have been able to perform it successfully in four instances.

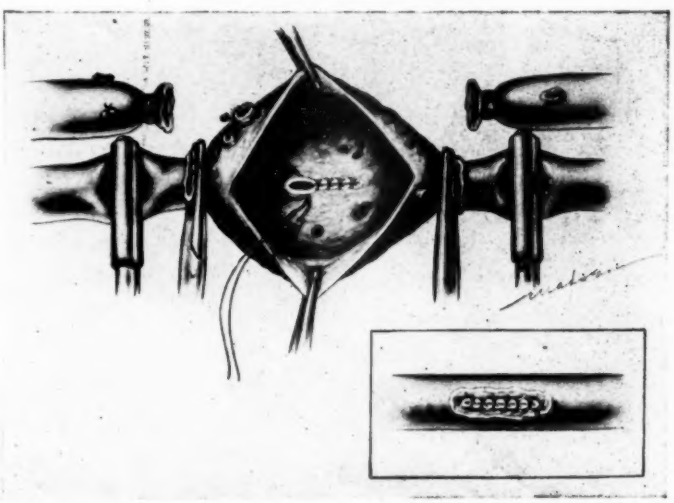

Fig. 2.—Repair of arteriovenous fistula through the sac. Vein has been ligated and divided. Insert shows excess sac excised.

III. *Ligation With Excision of All Involved Vessels.*—This operation usually gives the most satisfactory results. It takes advantage of the enormous collateral circulation which develops around an arteriovenous connection. I wish to point out that the term quadrilateral ligation is a misnomer. Rarely are there only four vessels involved. Collateral and new vessels form so rapidly and the vein and its branches dilate so quickly that innumerable vessels are encountered.

IV. *Obliteration Operation.*—In a few, obliteration similar to that used in arterial aneurysms is satisfactory.

ARTERIAL VARICES SYNDROME

We wish to draw attention to a group of patients often misdiagnosed and therefore inadequately treated. For a long time we have been aware that certain patients diagnosed as having varicose veins had pathology other than incompetent venous valves. Not infrequently adequate varicose vein surgery by competant surgeons has been followed by prompt recurrence. Careful observations have disclosed that such patients have innumerable small connections between the femoral artery and saphenous system (Fig. 3). This is not the simple aneurysmal varix in which one small artery branch dilates the saphenous vein, but is a congenital anastomosis by multiple small vessels which

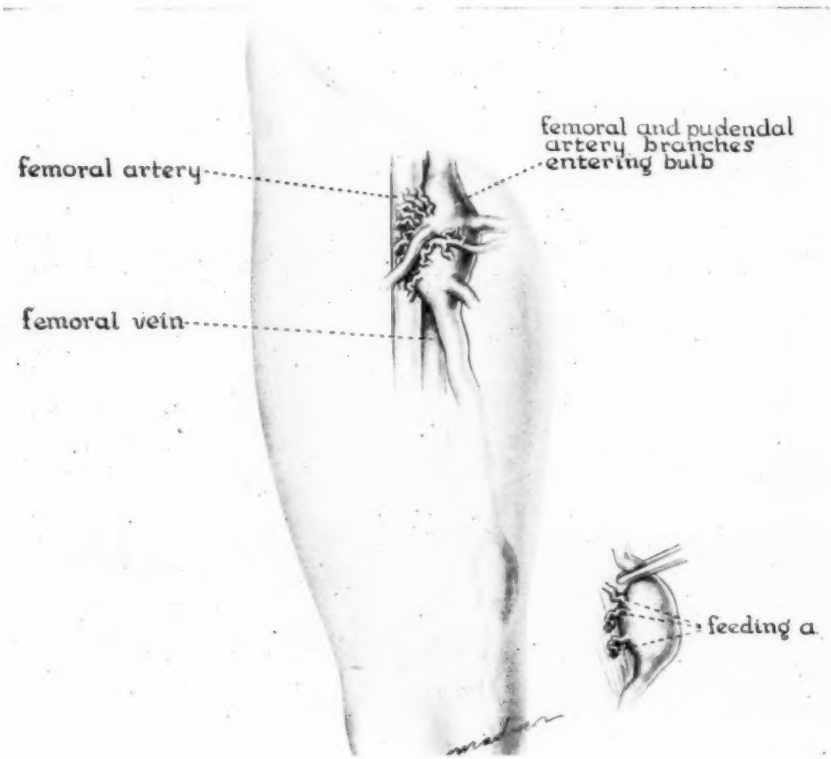

Fig. 3.—Drawing illustrating the anatomy of arterial varices.

suddenly open after having been obliterated for years. The diagnosis of this syndrome which we call arterial varices may be made by use of the following criteria:

1. The veins develop rapidly and extensively and remain partially filled on elevation of the limb. The vessels can be reduced on pressure but fill more rapidly than ordinary dilatations on a basis of valve failure.

2. The veins occur more often on the lateral aspect of the leg or in the popliteal space (Figs. 4 and 5).

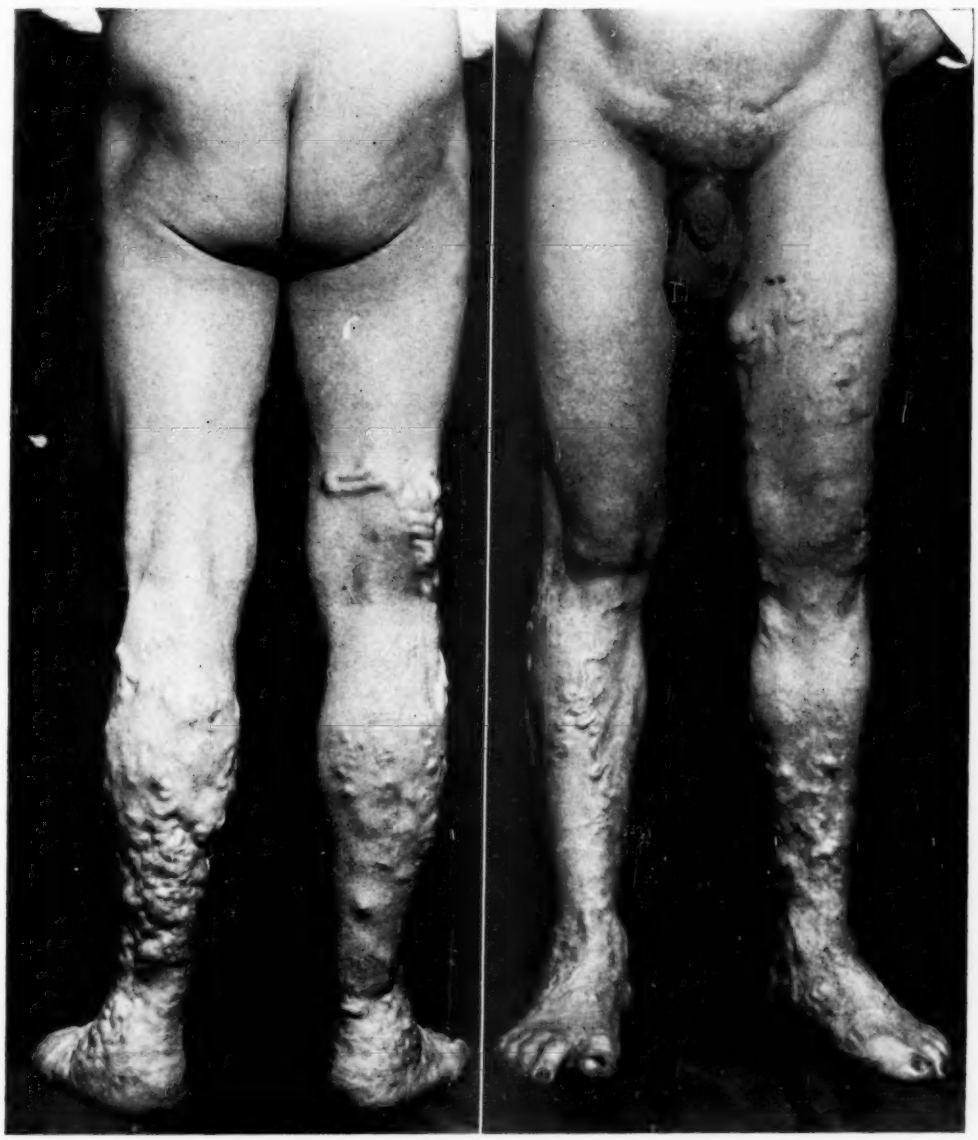

Fig. 4 *Fig. 5*

Fig. 4.—Typical appearance of arterial varices. These extreme dilatations appeared suddenly, unlike the slow development of varicose veins.

Fig. 5.—Anterior aspect of same patient as shown in Fig. 4.

3. They recur after the usual operation for varicose veins.

4. There is a greatly increased skin surface temperature which can be registered with the hand and always with the potentiometer.

5. There may be a bruit but usually this is not present. A bruit is caused by whirling blood. If the arteries are small and the vein large enough, the vein takes up the blood from the artery without the development of sufficient whirling to produce a bruit.

6. When the vein is opened, arterial blood is ejected synchronously with systole.

7. On pathologic section the vessel walls show more coats (Fig. 6) than a normal vein (Fig. 7) and less coats than an artery. This is the result of the reaction of the vessel to the circulatory trauma.

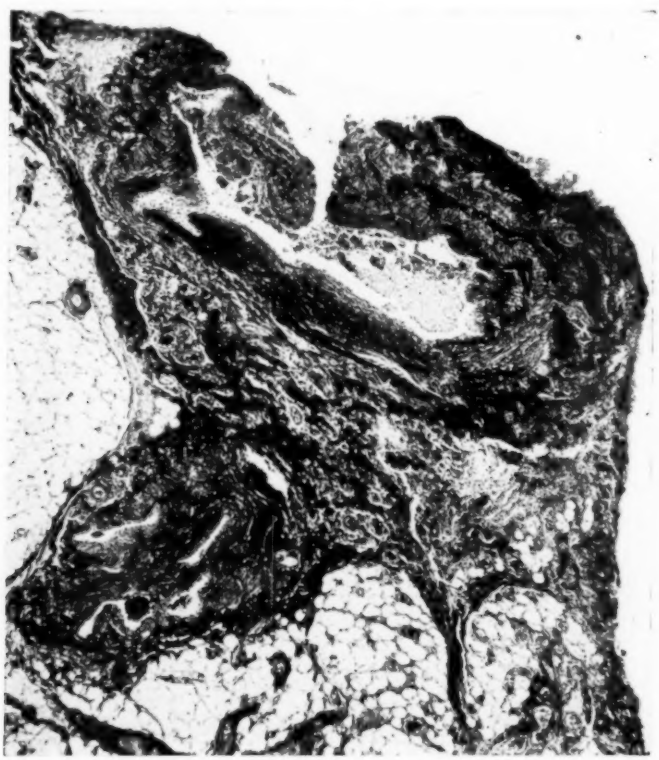

Fig. 6.—An arterial varix showing a vessel wall thicker than a vein. It does not have all the coats of an artery. Thickening is due to reaction of the vessel to arterial pressure (× 50).

8. Oxygen saturation of the blood in these veins is higher than in ordinary veins.

It is suggested that in questionable cases the veins be incised and observed for arterial pulsations.[20]

In the last 244 patients sent to us for varicose veins of a complicated nature, fifty-nine (almost 25 per cent) had varices which had recurred after operations performed by qualified surgeons. Of these fifty-nine patients, thirty-eight had arteriovenous connections. In the patients of this group in whom the varices were nonrecurrent, twenty-one had such connections. Thus, fifty-

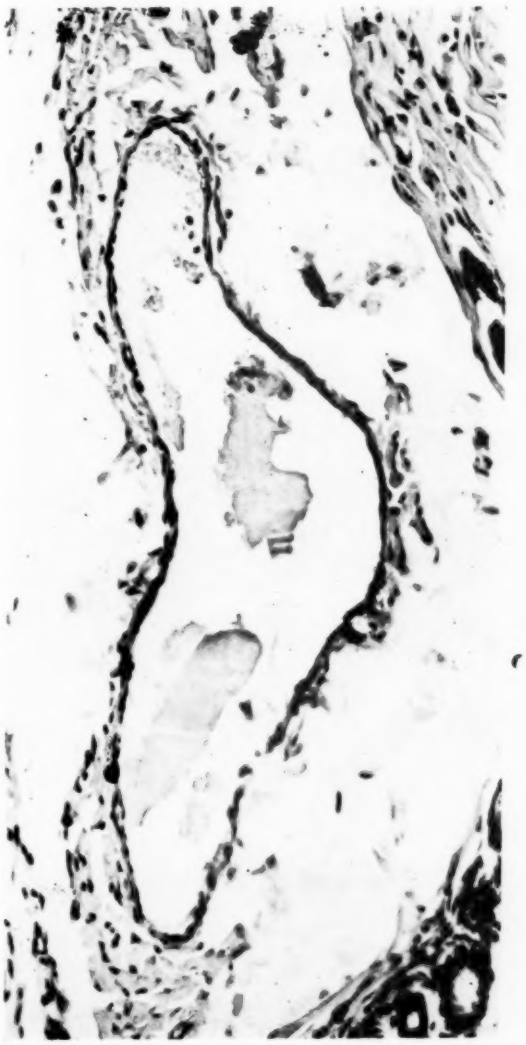

Fig. 7.—Photomicrographic section of a normal vein (× 260).

nine, or almost one in every four of those with advanced venous pathology, had undiagnosed arteriovenous connections rather than incompetent venous valves. It is difficult to obtain pathologic confirmation in all of these, since pathologists require certain walls to be present before they are willing to identify a vessel as an artery. In these fistulas, the vessel walls are usually im-

mature and poorly formed. Additional criteria for the pathologic recognition is being established.

Treatment of Arterial Varices.—The treatment requires:

1. Wide excision of the saphenous vein and its branches in the groin and popliteal space with resection of each arterial branch.

2. Excision of the saphenous vein at each incompetent point.

3. Extended and at times repeated excision of all dilated veins on the lateral aspect or popliteal area of the leg.

4. Inspection at six- to twelve-month intervals for recurrence points, and resection if they are large and injection if small.

SUMMARY

We wish to emphasize, the following:

1. The surgical treatment of arterial aneurysm must be individualized. Of the operations, the anastomosing or obliteration procedures potentially are the best. Obliteration of the aortic aneurysm is possible if certain technical difficulties are overcome.

2. Some arteriovenous aneurysms can be excised and anastomosed or the arterial defect sutured. In others quadrilateral ligation is not sufficient, but multiple resection of all the vessels involved in the process must be performed.

3. Congenital arteriovenous aneurysms may be quiescent for years, then become active and, like cancer, prove very difficult to eradicate. Neologically, arterionia is suggested.

4. A syndrome not emphasized before is presented. In this syndrome arteriovenous connections are misdiagnosed as varicose veins. This occurs in our practice in 25 per cent of those sent for advanced vein pathology. The syndrome of arterial varices can be diagnosed by attention to the features which have been pointed out. This syndrome should be suspected particularly if the veins are on the posterolateral or lateral aspect of the leg, if the patient is young, if there is increased local heat, and if the veins recur after adequate vein resection.

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PLASMA AND BLOOD INFUSION FOLLOWING MYOCARDIAL INFARCTION

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ACCOMPANYING or shortly succeeding myocardial infarction, a shocklike state with fall in both systolic and diastolic blood pressure has long been recognized as a frequent occurrence. Master and associates[1] studied 205 patients surviving attacks of acute myocardial infarction, 57 per cent of whom developed an abrupt fall of blood pressure within the first three days. This percentage included patients recovering from an immediate fall and exhibiting secondary depressions of their blood pressures. These authors conclude from the study of 538 patient-attacks that death generally occurred if the systolic blood pressure at any time fell below 80 millimeters of mercury. Likewise, if patients had been previously hypertensive, the fatality rate was materially elevated when the blood pressure fell below 100 mm. Hg, namely 50 per cent in that group, as contrasted to 29 per cent for the entire series. Mintz and Katz[2] reported a shocklike state in 6.9 per cent of 524 patients with acute myocardial infarction and a fatality rate of 77.8 per cent in the group with shock, as contrasted to 20 per cent in the entire series.

Even in such patients whose blood pressure returns spontaneously to more normal levels the occurrence of heart failure or death is frequent, indicating that extensive damage to the myocardium exists. However, certain patients recover and even maintain an adequately functioning myocardium. Recovery depends upon the availability of adequate circulation not only to the infarcted area but to the entire myocardium through all channels, including collateral arteries.

Recovery of an effective head of blood pressure in the aorta and the coronary arteries is essential, therefore, to prevent not only myocardial failure but also secondary myocardial infarction in areas supplied by narrowed arteries. Inadequate circulation elsewhere in the body, notably in the brain and the kidneys, is responsible for serious sequelae to myocardial infarction. Impairment of renal function has been generally found by the authors to follow myocardial infarction and in sustained hypotension has probably contributed to pulmonary edema and death in certain patients. Certain cases will be discussed later with illustrations. Reference is made to Case 1 (Fig. 2).

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The level of arterial pressure at which coronary blood flow becomes ineffective probably differs in each individual, as illustrated by the higher mortality in hypertensive patients, as contrasted to normotensive persons whose systolic blood pressure falls below 100 millimeters of mercury.[1] Thus, in a hypertensive woman (Case 5, Fig. 3), pallor, cyanosis, sweating, and faintness were present when her blood pressure fell from 186/120 to 96/68, whereas normotensive patients rarely exhibited such signs until the systolic blood pressure fell below 86 millimeters of mercury. Normally, hypotensive individuals may not show such evidence of circulatory insufficiency until their blood pressure reaches proportionately lower levels.

For these several reasons attempts have been made to correct the persistent severe hypotension of myocardial infarction by various means. Caffeine, Coramine, ephedrine, Paredrine, Neosynephrine, and epinephrine are among the drugs used, but the general clinical experience is that these substances are either ineffective or only transiently beneficial.

Transfusion has been performed by Gold,[3] Schwartz,[4] De La Chapelle,[5] Segal,[6] Levine,[16] and others as a means of elevating and sustaining the blood pressure. The objective of tranfusion is to correct the fall in blood pressure associated with the shocklike state of myocardial infarction but, in so doing, not further to handicap circulatory efficiency.

The cause of the shocklike state is not clearly established at present. Unknown hormonal and/or neurogenic factors may initiate this abnormal circulatory state. To what extent disturbed peripheral vascular functions contribute to it is not known.

There is a general belief, shared by Stead and Ebert,[7] Fishberg,[8] Murray,[9] Prinzmetal,[10] and Mendlowitz and his associates,[11] that there is diminished left ventricular output. This could be due to: (1) Diminished myocardial competence as evidenced by the occurrence at times of prolonged circulation time and elevated venous pressure. The inconstancy of these findings suggests either that their appearance is associated with definite degrees of incompetence or that there is a different causal mechanism which is not constantly operating in "infarction shock." (2) Depletion of effective circulating blood volume similar to that which occurs in hemorrhagic and traumatic shock. Hemoconcentration and hypovolemia generally occur in this state but do not occur concomitantly or in the same sequential degrees as the fall in arterial blood pressure. In two patients referred to by Stead and Ebert,[7] "shock" was not increased by therapeutic bleeding; this further suggests that faulty venous return was not responsible for the shocklike state. (3) Ballooning of muscle or an "expansion chamber" effect has been observed by Murray[9] and by earlier investigators to be inconstantly formed from the myocardium surrounding the infarct, as produced in dogs by ligation of the left anterior descending coronary artery. Such noncontractile zones, succeeding an attack of acute myocardial infarction and involving much larger areas of the heart muscle than the actual infarct, have been demonstrated in man by fluoroscopy and roentgenkymography by Dack and associates[12] and by others. Murray[9] demonstrated

in dogs an improvement in aortic blood pressure and in cardiac output by resecting this area with the infarct.

Prinzmetal and his associates[10] and Corday and co-workers[13] reported the development of similar inactive areas in dogs on ligating the left descending coronary artery. Such areas are inconstant and recurrent in the absence of shock but constant following hypoxia or hemorrhagic shock. By transfusion after hemorrhagic shock, these workers restored the blood pressures to normal, and this was followed by resumption of contractions in these dilated areas surrounding the infarcts. After hypoxia, resumption of normal oxygenation of the blood produced a similar effect.

In clinical myocardial infarction, sustained shock and presumably dilatation of ventricular muscle commonly occurs without a complicating factor such as the bleeding used by Printzmetal. However, the conditions are sufficiently similar to suggest that increasing the volume of blood entering the heart may have a beneficial result in human myocardial infarction. Thus, by obtaining better filling of the dilated chamber, a larger output would be expected according to Starling's law. None of these theories is uniformly supported by the available data, but at least certain hemodynamic conditions already referred to[2,3] are known to be improved by transfusion.

Indications for Intravenous Infusions.—The development of pallid cyanosis, faintness, sweating, and abrupt fall in blood pressure or critical hypotension were the indications which led us to resort to infusion in the patients with myocardial infarction whose cases are being presented. Thus, the blood pressures at the time of the first infusion varied from 55/40 to 88/58.

In Case 6, one transfusion, and in Case 7, three additional transfusions were given on successive days after recovery from the initial shock in an attempt to sustain presumably effective blood pressure (88/64 to 100/76). A rise of systolic blood pressure of 16 mm. Hg or more was considered a successful result and this was invariably maintained for three and one-half hours or more.

Dangers of Intravenous Infusions.—The possible dangers of infusion would appear to be (1) the abrupt overloading of the left ventricle, especially in the presence of marked pulmonary edema, and (2) increasing right ventricular failure as evidenced by markedly elevated venous pressure. The rate and amount of infusion as well as the selection of patients for this procedure should be governed by an appreciation of these dangers.

It is likewise recognized that inadequate amounts of blood or plasma or too slow a transfusion rate would not materially modify hypovolemia or faulty circulatory dynamics. Too long a delay in instituting transfusion as well as slow rate of delivery of blood are well recognized causes for failure to reverse hemorrhagic shock[14,15] These may be causes of failure of transfusion to alter the shocklike state of myocardial infarction.

METHOD AND RESULTS

Eleven patients, seven men and four women, ranging in age from 44 to 65 years, were given thirty blood and whole plasma intravenous infusions by the gravity method (Table I). The location of the infarct, as diagnosed by the electrocardiogram and in five of the cases by electrocardiogram and autopsy findings, was in the anterior wall and septum of the left ventricle in four cases and in the posterior wall and septum of the left ventricle in seven. Five patients, including the four women, had essential arterial hypertension. Four had had previous myocardial infarctions, two anterior in both episodes, one anterior with a previous posterior, and one posterior with a previous anterior. Two patients had a history of angina pectoris and five had had no symptoms of coronary circulatory insufficiency. None of these factors apparently influenced the degree of success of infusion nor the duration of life after this procedure.

Twenty-two citrated whole blood and eight pooled human plasma* infusions were used. Two patients were given one transfusion, four were given two, two were given three, one was given four, and two were given five transfusions. Five hundred milliliters were given six times, 375 ml. once, 300 ml. once, 250 ml. twenty-one times, and 175 ml. once. Five were given at rates of 1.0 to 1.9 ml. per minute, fourteen were given at rates of 2.0 to 2.9 ml. per minute, three were given at 3.0 to 3.9 ml. per minute, seven were given at 4.0 to 5.0 ml. per minute, and one was given at a rate of 8.3 ml. per minute. No untoward febrile or other reactions occurred within six hours after the infusions.

Only one of the eleven patients recovered and was discharged from the hospital as asymptomatic. However, three patients had abrupt deaths after recovery from "shock": Case 4 after nine hours, Case 8 after eight days, and Case 11 after three days. Case 5, a formerly hypertensive woman with nephrosclerosis, died with progressive pulmonary edema. Her blood pressure ranged from 112/80 to 140/96 for six days prior to death.

Four patients had only a single episode of hypotension. Of these, three were unaffected by transfusion and death supervened. Three patients had two episodes. In at least one instance in each patient this was improved by infusion, and one patient spontaneously recovered from another. Three patients had three episodes, in all of which infusion was effective at least once, and in one of these three patients spontaneous recovery occurred twice. One patient had four episodes; the first three episodes responded transiently to infusion, the response lasting from three and one-half to nine hours. The fourth episode was not treated; hypotension persisted and resulted in death after twenty-four hours.

Of the twenty-three separate episodes of hypotension, five terminated in spontaneous recovery, eleven responded to infusions, and seven ended in death.

*Standard Army and Navy package. Normal human plasma, dried, with pyrogen-free distilled and sterilized water; representing 250 c.c. or 500 c.c. original normal plasma. One-tenth per cent WV citric acid and 1:50,000 phenyl mercuric borate added.

TABLE I. EFFECT OF BLOOD AND PLASMA INFUSION IN ELEVEN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

CASE	LOCATION OF INFARCT	PREVIOUS INFARCT OR ANGINA PECTORIS	PRIOR BLOOD PRESSURE	BLOOD PRESSURE AT INFUSION*	BLOOD PRESSURE AFTER INFUSION	BLOOD PRESSURE SUSTAINED THREE HOURS†	DURATION HYPOTENSION BEFORE INFUSION (HR.)	RATE OF INFUSION (ML. PER MIN.)	AMOUNT OF INFUSION (ML.)	INFUSIONS EFFECTIVE (16 MM. Hg. +) +	INFUSIONS EFFECTIVE (16 MM. Hg. +) −	SURVIVAL AFTER FIRST INFUSION: 3-15 HR.	48-72 HR.	72 HR.-4 DAYS	8 DAYS	DISCHARGED ALIVE
1 (L. S., M., 55)	Ant.	Post.	120/82	70/53	90/70	+ 4 hr.	1	3.7	500P	3			X			
2 (H. C., M., 56)	Post.	0	165/100	72/40	72/50	−	11	4.2	250B	2		X				
3 (I. C., M., 60)	Post.	Ant.	110/80	(80/64)-70/?	94/70	+ 9 hr.	2½, 18, 20	2.1, 3.3, and 4.2	250B, 250B 250B	1 4 (No. 3)			X			
4 (D. S., M., 62)	Post.-Lat.	0	112/70	(88/58)-60/42	90/60	+ 3 hr. 40 min.	¼	3.1	250B	2		X				
5 (H. B., F., 65)	Post.	0	200/124	84/64	110/64	+ 3 hr. 30 min.	1½	2.0	175B	1 2 (No. 1)					X	
6 (R. R., F., 61)	Post.	0	170/100	74/60	98/78	+ 36 hr.	2½	2.8	250P	1 1 (No. 1)				X		
7 (H. W., M., 44)	Post.	0	110/72	(84/40)-74/50	92/66	+ 5 wk. +	1½	2.4	250B	1 4 (No. 2)						X
8 (L. R., F., 62)	Ant.-Sept.	Ant.	164/104	55/40	108/70 (Caffeine S.B. IV)	+ 23 hr.	½	4.1	250P	1 1					X	
9 (W. W., M., 49)	Ant.-Lat.	Ant. (2)	124/86	82/60	86/60	−	58	2.4	250B	4				X		
10 (M. L., M., 44)	Post.-Lat.	Ang. pect.	140/90	86/68	102/80-60/?	0	4	5.0	250P	1		X				
11 (M. B., F., 62)	Ant.	Ang. pect.	164/112	74/60	86/60-94/70 (½ hour)	+ 3 days	½	4.2	500B	1			X			

*The blood pressure is given in millimeters of mercury. Figures in parentheses are the initial pressures recorded at onset of the hypotension.

†The plus (+) sign indicates at least one "effective" infusion. The minus (−) sign indicates no "effective" infusion. The zero (0) sign in Case 10 indicates a transient effect, which was followed shortly by death.

In all cases except Case 3, where the data on three infusions are given, the data in Columns 6 through 10 represent the results of the first "effective" infusions, or, if ineffective, the first infusions given.

Bilateral pulmonary râles were present in eight of the eleven patients at the time of one or more of the infusions. They were limited to the lower lung bases in all patients but one (Case 10), in whom they were hilar and basal and coarser than subcrepitant in quality.

In seven instances no change occurred in the intensity of the pulmonary edema within three hours after infusion; in three the râles diminished; and in two (Cases 1 and 6) on the second infusion, with the blood pressure sustained at 94/78, they increased slightly. In Case 10, to be reviewed later, there was no increase in the moderately severe pulmonary edema, but the patient lapsed into coma at the completion of transfusion. The blood pressure fell after a transient rise and he died three hours later. This patient had an initial venous pressure of 24 cm. of isotonic sodium chloride solution.

In eight of the eleven patients at least one infusion produced a successful result. Where successful elevation of blood pressure was obtained in the seven patients receiving more than one infusion, this occurred in the first infusion in five cases, and in the second and in the third infusions in one case each where prior infusions had failed.

The percentages of success with 500 and 250 ml. of blood or plasma seemed to be the same. In Case 8 a rise of blood pressure of 10 mm. Hg occurred after 100 ml. of blood had been given; in Case 5 a rise of 26 mm. Hg with a total of 175 ml. of blood; and in Case 10, with a high initial venous pressure of 24 cm. of normal salt solution, a rise of 26 mm. Hg took place with 100 ml. of blood given in twenty-five minutes.

Table II presents the infusions resulting in significant rises and maintenance of blood pressure. There were three instances of systolic pressure elevations of 16 to 18 mm. Hg, seven of from 20 to 30 mm. Hg, and one of 53 millimeters of mercury. In two instances transfusion produced no significant rise of diastolic pressure, in five transfusion produced a rise of from 10 to 15 mm. Hg, in three a rise of from 15 to 20 mm. Hg, and in one a rise of 30 millimeters of mercury.

TABLE II. DEGREE OF DURATION OF SIGNIFICANT ELEVATION OF BRACHIAL ARTERIAL BLOOD PRESSURE FOLLOWING ELEVEN BLOOD OR PLASMA INFUSIONS

Systolic blood pressure elevation (mm. Hg)	16	18	20	24	26	30	53	
Number of instances	1	2	4	1	1	1	1	
Diastolic blood pressure elevation (mm.Hg)	0	2	10	14	16	18	20	30
Number of instances	1	1	3	2	1	1	1	1
Duration of sustained elevation of systolic blood pressure	3½° to 4°		6°	7°	9°	22°	39°	72°	5 wk. +
Number of instances	3		1	1	2	1	1	1	1

The maintenance of the elevated blood pressure was observed from three and one-half to four hours in three instances, from six to nine hours in four instances, from one to three days in three instances, and to the time of discharge after five weeks in one patient.

The packed cell volume seemed to vary in the individual patients with the degree of "shock" exhibited and invariably increased with advancing heart failure and pulmonary edema. Six of ten patients exhibited a packed cell volume of over 47 c.c. per cent within twenty-four hours of hospital admission. Thus, Case 3 with relatively little shock at entry had a packed cell volume of 39 c.c. per cent, whereas Case 2 with severe hypotension initially had 51 c.c. per cent, which rose to 55 per cent before death.

Total serum protein varied from 5.5 to 6.8 Gm. per cent in the five cases in which determinations were made. Only minor changes were noted in the packed cell volume and total protein following infusion in six cases so studied. For example, Case 1 had a packed cell volume of 56 c.c. per cent one hour before a 500 ml. plasma infusion and a total protein of 6.8 Gm. per cent. Two hours after transfusion there was a packed cell volume of 60 c.c. per cent and a total protein of 6.7 Gm. per cent. Fourteen hours later, one and one-half hours after a 250 ml. transfusion of blood, the determinations were 50 and 5.8, respectively, and twenty-four hours later, after another 250 ml. blood transfusion, the packed cell volume was 54 c.c. per cent and the total serum protein was 6.5 Gm. per cent.

Changes such as were observed cannot at present be assigned solely to the infusions because fluctuations in the degrees of heart failure and altered peripheral vascular dynamics probably occurred and influenced the packed cell volume and protein concentrations.

In four patients in the recumbent position determinations of venous pressure by direct measurement were made in the antecubital vein, immediately prior to and following five infusions. The results show that little elevation follows when venous pressure is not over 13 cm. of normal salt solution. Case 1, receiving 250 ml. of blood at a rate of 2.5 ml. per minute, demonstrated a rise from 13 to 17 centimeters. Case 9 showed on the second transfusion a rise from 8 to 11 cm. with 250 ml. of blood at 1.7 ml. per minute and on the third transfusion, no significant change, namely 10.5 to 11 cm. after 250 ml. of blood at 1.4 ml. per minute. The rate of transfusion in this patient was probably too low since the arterial blood pressure actually fell during both transfusions. The circulation time, arm-to-tongue, was unchanged at thirty-five seconds on the second transfusion and was thirty-seven seconds prior to and forty seconds following the third transfusion, confirming the unaltered state of vascular congestion.

Case 11 illustrated that a 500 ml. blood transfusion at 4.2 ml. per minute had no effect on the venous pressure, which was 9.2 cm. prior to and 9 cm. following the treatment. The arterial blood pressure rose from 72/60 to 94/70 in the same period of time.

Case 10 (Fig. 6) was an example of the probably harmful influence of infusion in a patient with a high venous pressure and marked pulmonary edema.

An infusion was given because his blood pressure, which had been 110/70 on the fifth day after the onset of the myocardial infarction, fell to 84/72 on the sixth day. The low blood pressure was accompanied by chest pain, pulmonary edema, and cyanosis, and failed to rise after the intravenous administration of 1.0 Gm. of caffeine and sodium benzoate.

The circulation time in Case 10 was seventeen seconds and the venous pressure, 24 cm. of normal salt solution at the start of the infusion of 250 ml. of plasma at 5.0 ml. per minute. After 100 ml. had been given the venous pressure was 26.5 cm. and the blood pressure was 102/80. After completion of the infusion in fifty minutes, the venous pressure was 37 cm., and the blood pressure was 88/70, and although the cyanosis was somewhat lessened and the pulmonary râles had not increased, the patient lapsed into coma. The heart sounds, which had become louder during the infusion, became inaudible ten minutes later and the blood pressure fell to 62/50. The patient died two hours later without regaining consciousness.

From this case history it may be assumed that a high venous pressure is evidence of adequate venous return and that only harm can result from further addition to the blood volume. Although death may have been coincidental, in as much as circulatory failure was advancing rapidly at the time of the infusion, it is likely that the cardiac failure was hastened by that procedure.

Comment.—Three factors seem to be important in gaining an effective elevation of blood pressure by infusion, namely (1) early institution of the procedure after the onset of hypotension, (2) a sufficiently rapid rate of transfusion, and (3) the degree of hypotension. The influence of the first two of these factors may be illustrated by Fig. 1, in which the thirty infusions are graphically shown in relation to the rate of infusion and the time elapsed after onset of each episode of hypotension for which the treatment was given. In ten of the eleven patients in whom successful results were obtained the transfusions were given within four hours of the onset of marked hypotension; in only four of the nineteen patients in whom the procedure was unsuccessful were the infusions given within this period. The successful transfusion in Case 3, recorded as having been given twenty hours after onset of hypotension, actually followed by two hours a similar transfusion of 250 ml. of blood and produced a sustained elevation of blood pressure for nine hours.

In the three failures where treatment was given four hours or less after onset of "shock" the infusions were given at rates of 4.6, 2.1, 1.7, and 1.4 ml. per minute, respectively. All of the successful infusions were given at rates over 2.0 ml. per minute and seven of the eleven were given at rates of from 2.5 to 4.3 ml. per minute. In Case 8, a woman with long-standing hypertension, the second transfusion was given when the blood pressure was fluctuating between 92/58 and 110/76, and was resorted to not only in an attempt to stabilize the pressure but also because of dehydration and inanition accompanying anorexia and nausea. No immediate ill effect followed this infusion, which was administered at a rate of 8.3 ml. per minute, although pulmonary edema developed ten hours later following a hypodermoclysis of 1,000 ml. of normal salt solution.

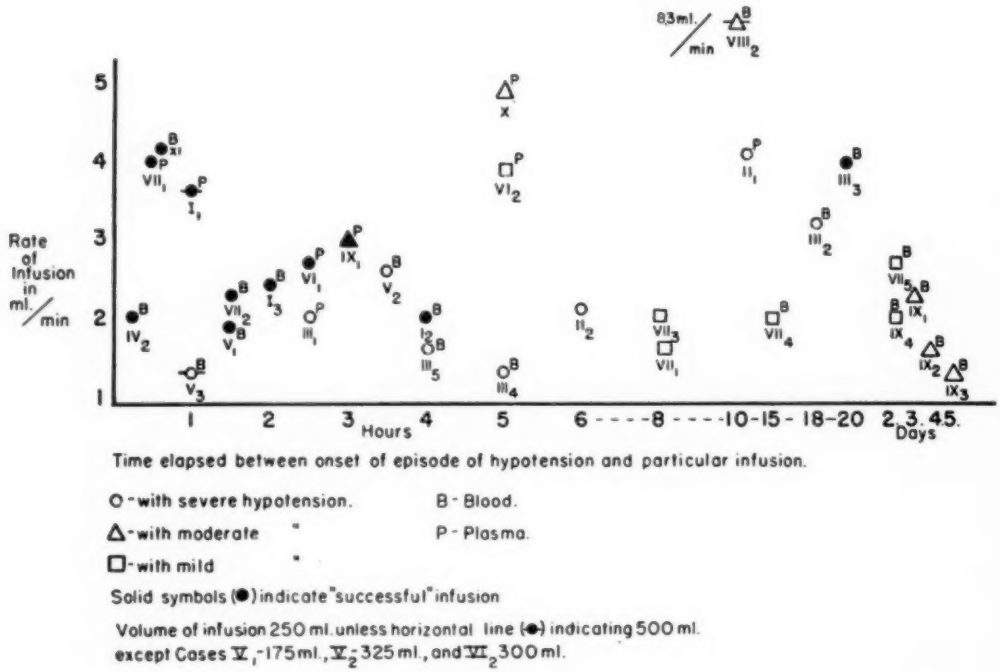

Fig. 1.—Relation of success of intravenous infusion to rate of flow and to duration of hypotension prior to start of infusion. Roman numerals indicate case number; Arabic numerals, the number of infusions in each particular case.

The patients who responded best to infusion were, in general, those with the most severe hypotension. Thus, of the eleven patients in whom infusions gave "successful" results, nine had initial systolic blood pressures of 80 mm. Hg or less, and the remaining two had pressures of 84 and 88 mm. Hg, respectively. The former was a woman with previous severe hypertension (Case 5). Of the nineteen patients who were classified as failures, seven had initial systolic blood pressures of 82 mm. Hg or lower, four had pressures of from 86 to 88 mm. Hg, and eight had pressures over 90 millimeters of mercury. In Case 7 (Fig. 4), three of the four infusions were given largely to sustain blood pressure, and in Case 9 the symptoms of shock were more evident that the preinfusion blood pressures (88/60, 100/70, 92/70, and 82/76 mm. Hg) indicated.

Certain of the case findings are illustrated in Figs. 2 to 6 (Case 1 in Fig. 2, Case 5 in Fig. 3, Case 7 in Fig. 4, Case 8 in Fig. 5, and Case 10 in Fig. 6).

Case 1 illustrates three successful responses to infusion, but the failure to sustain the blood pressure more than seven hours at any time led to cessation of treatment. Perhaps continued infusions might have resulted in recovery.

Case 5 demonstrates two ineffective transfusions following ten hours after a small but apparently successful one. This patient recovered from "shock" but later died from progressive pulmonary edema. In spite of low plasma

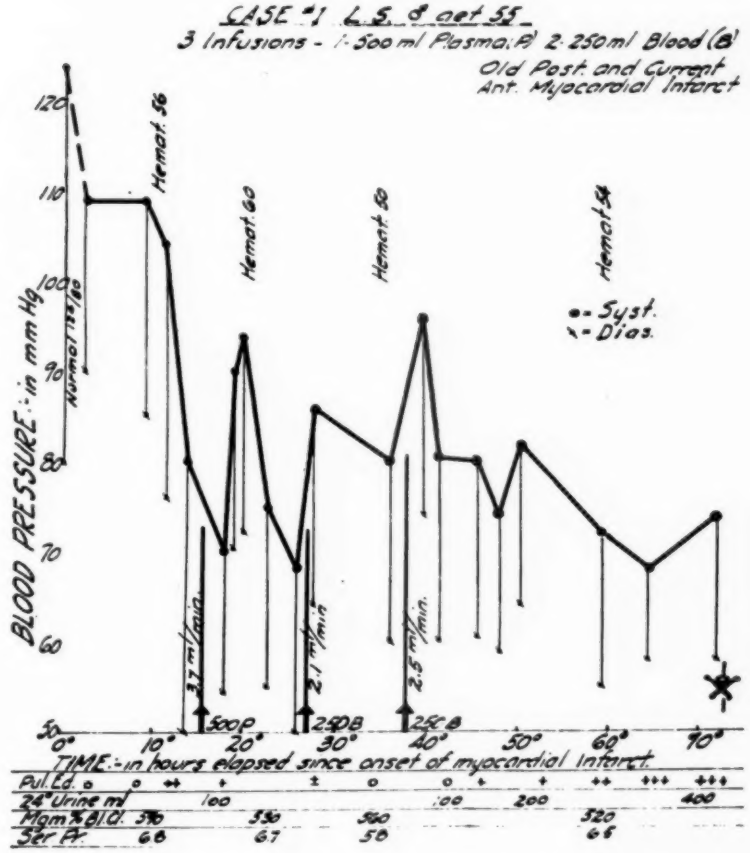

Fig. 2.—Response of blood pressure to infusions in Case 1. Additional data on occurrence of pulmonary edema, total urine output in indicated periods, and plasma chlorides and serum protein at various times after the onset of myocardial infarction.

chlorides, the retention of sodium, which was augmented by hypodermoclyses of normal salt solution and glucose, was probably partially responsible for this fatality.

Case 7 illustrates a spontaneous recovery from shock, a second episode with successful response to transfusion, and then the maintenance of moderate but constant hypotension following three additional transfusions. This man recovered to leave the hospital asymptomatic.

Case 8 illustrates a striking effect of early transfusion. This may have been aided by intravenous caffeine and sodium benzoate given in a dose of 1.0 Gm. one-half hour before the infusion of 250 ml. of blood, but it was unlikely that caffeine produced the sustained effect exhibited. This patient would probably have survived, as the evidences of shock were absent for six days, if a secondary myocardial infarction had not supervened.

Case 10 illustrates the harmful effect of infusion when a high venous pressure exists.

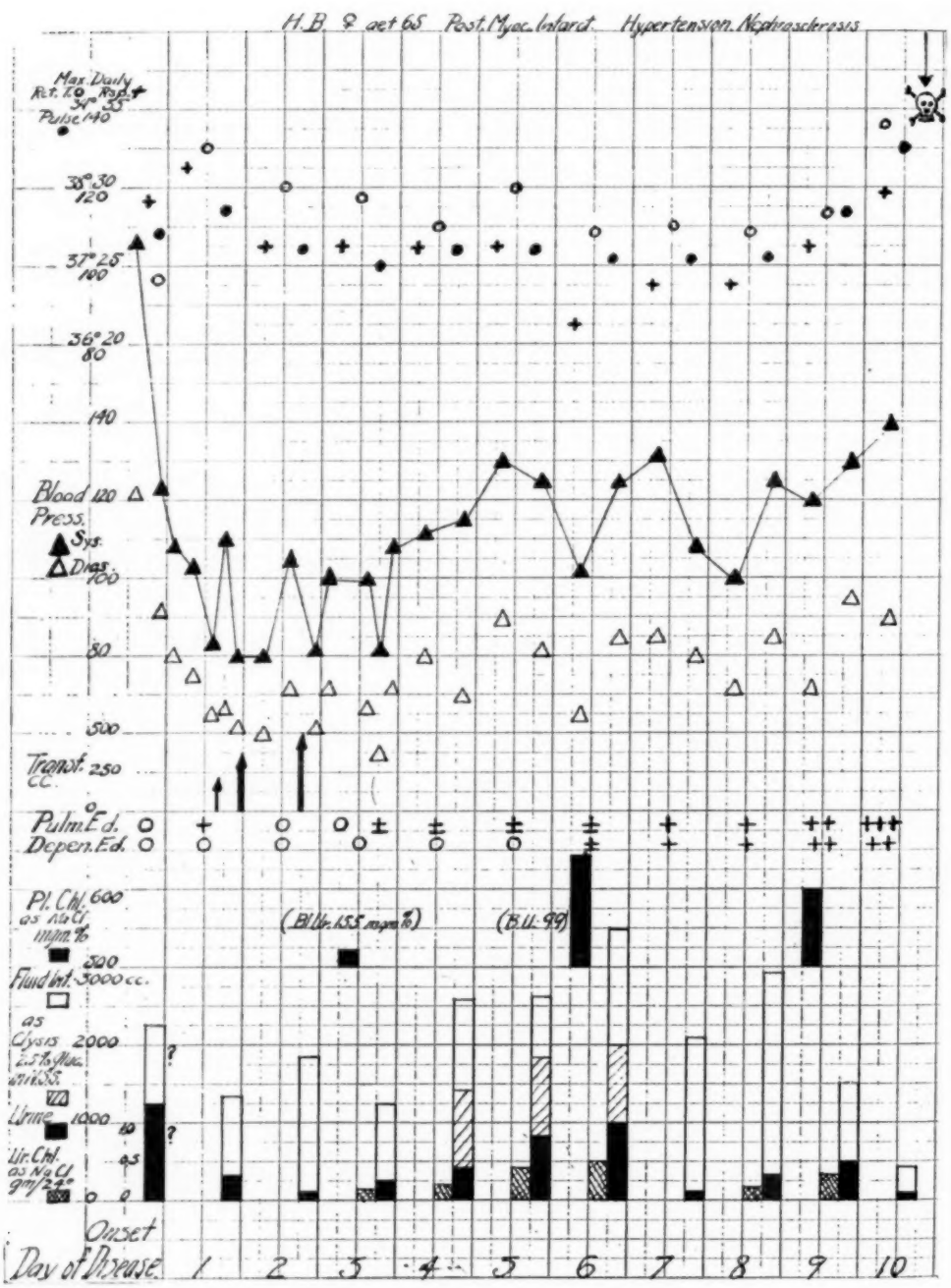

Fig. 3.—Response of blood pressure to infusions in Case 5. Clinical data as in Fig. 1 with daily fluid intake and urine output and urine chlorides, plasma chlorides, and blood urea at various times after the onset of myocardial infarction.

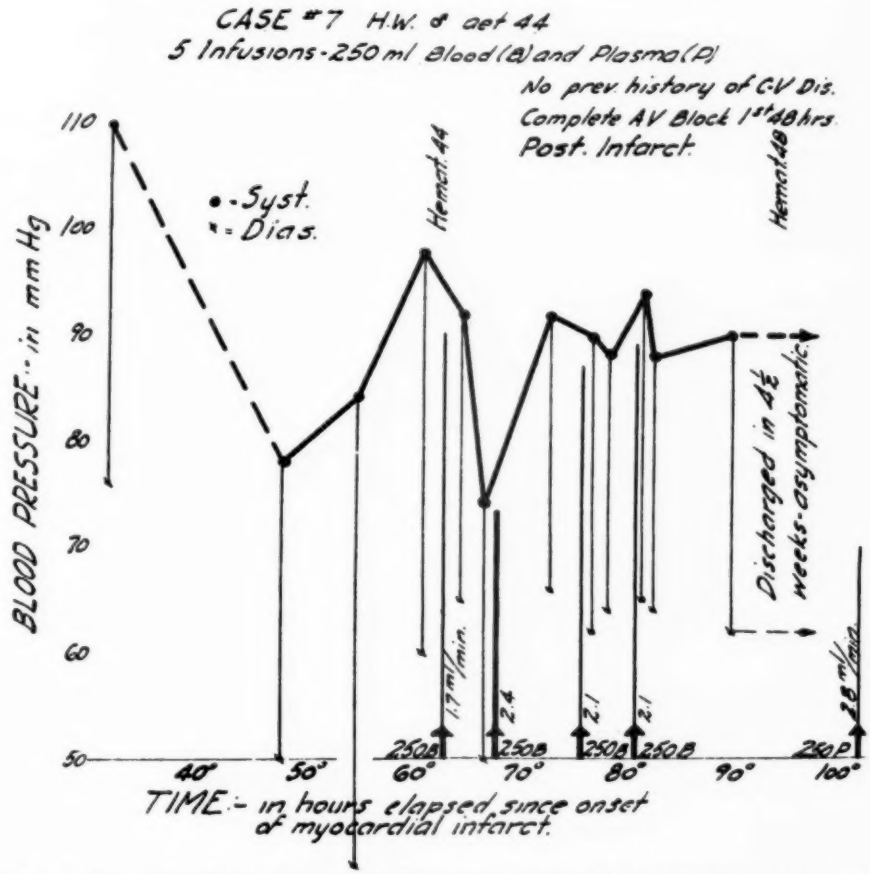

Fig. 4.—Response of blood pressure to infusions in Case 7. Note that the first infusion was ineffective, the second was effective, and the third and fourth infusions were given in an attempt to maintain elevated blood pressure.

Case 11 is an example of another effective elevation of blood pressure following blood infusion, which was sustained for a sufficiently long period to conclude that this patient would probably have survived the initial attack of myocardial infarction if a secondary attack had not occurred (not illustrated).

DISCUSSION

It is recognized that the reasons are not well established for the success or failure of blood or plasma infusions to elevate effectively or to sustain blood pressure through a critical period following myocardial infarction with eventual survival of the patient. Perhaps the regime employed in Case 7, repeating infusions after an initial satisfactory response, without recurrent severe shock may result in more survivals. The indications for such repeated transfusions as well as for the mode of administration of the individual infusion will probably depend on the development and application of techniques for more exact study of the blood volume, cardiac output, and pulmonary and peripheral circulation than have been pplied to this series of patients.

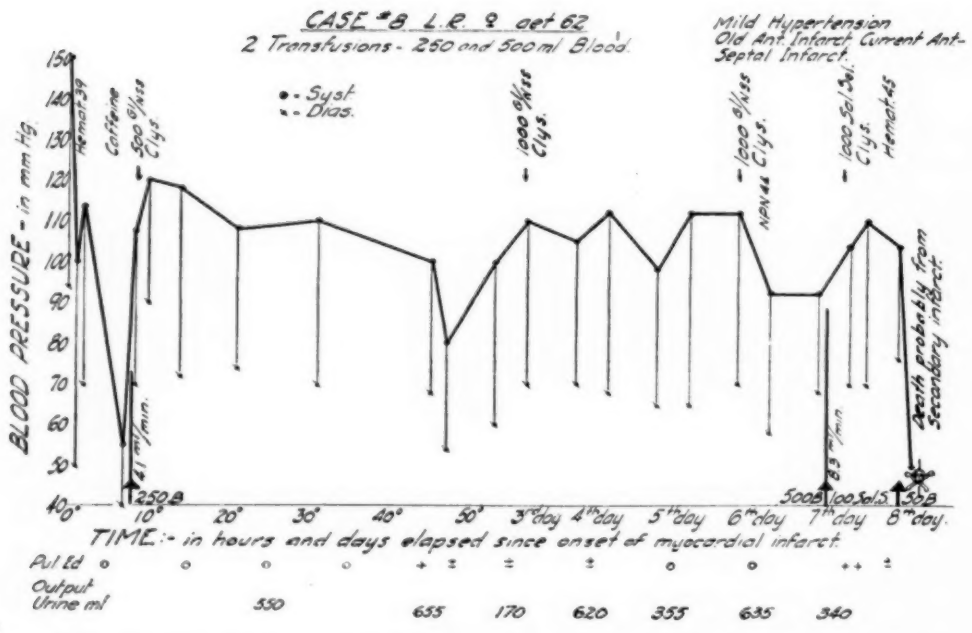

Fig. 5.—Response of blood pressure to infusions in Case 8. Note that recovery from "shock" followed the first blood infusion and no serious shock occurred until the abrupt fatal attack seven days later.

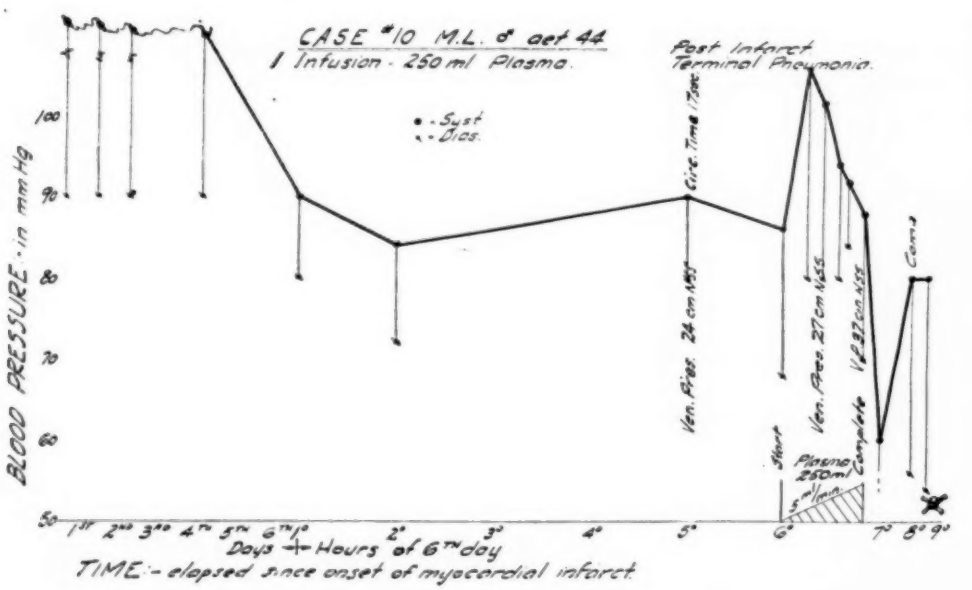

Fig. 6.—Response of blood pressure to plasma infusion in Case 10. Shock first occurred on the sixth day of illness. The venous pressure was high at the start of infusion, and whereas a transient rise of blood pressure followed the first 100 ml. of infusion, the patient's failure rapidly progressed to death.

SUMMARY AND CONCLUSIONS

Thirty intravenous infusions of blood and normal human plasma were given to eleven patients exhibiting one or more shocklike episodes following acute myocardial infarction.

Whereas only one of the eleven patients recovered and was discharged asymptomatic, the results of the infusions seemed to have carried four of them over critical periods of hypotension, and death resulted later from secondary infarction or heart failure.

No apparent harmful effects of infusion of blood or plasma were demonstrated except in a single patient with a high initial venous pressure. The infusions seemed to be more effective when the systolic blood pressure was under 85 millimeters of mercury. They were likewise more effective when given prior to four hours after marked hypotension developed and at rates of at least 2.0 and preferably of from 2.5 to 5.0 ml. (or 8.0 ml.) per minute.

It is assumed that the use of blood or plasma infusions probably cannot alter the immediate destruction of the myocardium by ischemia and that death will follow such destruction when it is extensive. However, the favorable effects may be due to (a) reduction of the effects secondary to shock (improved irrigation of the coronary bed); (b) maintenance of normal or excess venous return to the heart to preserve cardiac output in the presence of the dilated left ventricle; (c) reduction of the area of dilatation of the myocardium surrounding the infarcted zone, a process which may possibly cause or increase the shocklike symptoms and hypotension.

One cannot predicate that all of the successful results were due to the infusions since spontaneous recovery of hypotension after myocardial infarction is common. However, the prompt response in most instances seems conclusive of a genuine therapeutic effect.

ADDENDUM

Six additional cases of infusion treatment of myocardial infarction shock have been observed since presentation of this paper. Four improved, three of whom were discharged as recovered.

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THE SOUNDS AND MURMURS IN COARCTATION OF THE AORTA

A Study by Auscultation and Phonocardiography

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INTRODUCTION

CONSIDERABLE interest in the diagnosis of coarctation of the aorta has recently been stimulated by the successful surgical treatment of this condition. Although the murmurs which have been found in cases of coarctation of the aorta have been thought to be unimportant, the first suspicion of a congenital defect of the cardiovascular system is frequently aroused by the discovery of an abnormality on auscultation, and it is probable that further knowledge of the characteristic murmurs found in patients with this particular congenital defect will increase the frequency and accuracy of its diagnosis. With this objective in mind we have made, by auscultation and by phonocardiography, the following study of patients with coarctation of the aorta.

AUSCULTATORY SIGNS

Abbott,[1] in a comprehensive review of the literature up to 1928 on the subject of coarctation of the aorta, states that "a systolic murmur with maximal intensity along the left sternal border and heard also in the back, which is thought to be generated at the constriction, has been described (Laubry) as characteristic." She believes that other auscultatory abnormalities are caused by associated valvular lesions or are produced in the dilated and tortuous collateral channels.

A recent review of the subject by Reifenstein, Levine, and Gross[2] describes a systolic murmur over the precordium, especially at the base, and often in the back between the scapulae and alongside the lower dorsal spine. However, they consider that a systolic murmur in the back accompanying a murmur of only moderate intensity anteriorly is more diagnostic of coarctation of the aorta. Especially is this so in the rare instances when the murmur is louder behind than in front. They state that a diastolic murmur is not found in uncomplicated coarctation of the aorta and that when present it is associated with aortic valvular deformity or patency of the ductus arteriosus.

Taussig[3] maintains that there is no cardiac mechanism in this condition to cause precordial murmurs or thrills, which are, according to her, the exception

rather than the rule. She states, however, that the occurrence of murmurs in unusual places, as over any of the vessels of the collateral circulation, is characteristic of coarctation of the aorta, and that not infrequently the occurrence of a murmur in the interscapular region first suggests the possibility of this defect.

Our observations on a small series of patients indicate that there are certain auscultatory features which have not been adequately described. We have studied the patients by phonocardiography in order to illustrate these features and also to demonstrate that there are characteristics of the sound vibrations occurring in coarctation of the aorta which are not recognized by auscultation.

AUSCULTATORY FINDINGS

The material from which this study has been made consists of auscultatory and phonocardiographic findings on fifteen patients with coarctation of the aorta in whom surgical cure had not been undertaken (Table I). The coarctation was considered to be uncomplicated in these patients, except for one in whom the additional diagnosis of aortic regurgitation was made clinically.

A systolic murmur over the precordium was heard in all the patients except one (in this patient no murmur was heard over the anterior chest). The murmur ranged in intensity from slight (Grade 2) to very loud (Grade 5). Its maximal intensity was at the base of the heart in eleven patients and at the apex of the heart in one patient, while it was of equal intensity at apex and base in two patients.

A systolic murmur over the back was heard in every instance. This murmur was maximal either at the midline or a few centimeters to one or the other side of the midline at some level between the second and fifth spinous processes. It was of greater intensity over the back than over the precordium in five patients (one of these being the patient in whom no murmur at all was heard in front).

A diastolic murmur over the base of the heart was heard in five of the fifteen patients. *A diastolic murmur over the dorsal spine* was heard in four of these five, and in two of them the murmur was of greater intensity over the back than over the precordium. In two additional patients a diastolic murmur was heard over the back while none was audible in front.

We have described earlier the opinions of authorities who believe that precordial murmurs are the exception rather than the rule, and that diastolic murmurs are never present in uncomplicated coarctation of the aorta. However, the murmurs of complicating deformities such as aortic stenosis and insufficiency and patent ductus arteriosus are not well conducted to the back, and we have not found significant murmurs over the collateral channels in the patients under our consideration. Therefore, we consider that systolic and diastolic murmurs over the dorsal spine, where they are not infrequently of

TABLE I. FINDINGS IN FIFTEEN PATIENTS WITH COARCTATION OF THE AORTA

PATIENT	SEX	AGE	AUSCULTATORY FINDINGS						PHONOCARDIOGRAPHIC FINDINGS			
			PRECORDIUM			BACK			PRECORDIUM		BACK	
			INTERCOSTAL SPACE AT WHICH MURMUR HAD MAXIMAL INTENSITY	SYSTOLIC MURMUR	DIASTOLIC MURMUR	SPINOUS PROCESS AT WHICH MURMUR HAD MAXIMAL INTENSITY	SYSTOLIC MURMUR	DIASTOLIC MURMUR	SYSTOLIC VIBRATIONS	DIASTOLIC VIBRATIONS	SYSTOLIC VIBRATIONS	DIASTOLIC VIBRATIONS
L. M.	M	7	Second left	Grade 3	None	D 2	Grade 1	None	Present	Absent	Present	Present
J. T.	M	9	Second left	Grade 3	None	D 4	Grade 3-4	None	Present	Present	Present	Present
T. S.	M	11	Third left	Grade 3	Present	D 3	Grade 2	Present	Present	Absent	Present	Present
N. G.	M	19		None	None	D 2	Grade 2	None	Present	Absent	Present	Present
J. B.	M	22	Second left, apex	Grade 2	Grade 2	D 5	Grade 3	Grade 1	Present	Present	Present	Present
A. L.	M	22	Second right	Grade 3	None	D 3	Grade 2	None	Present	Present	Present	Present
A. C.	M	27	First left	Grade 2	None	D 2	Grade 2	Present	Present	Present	Present	Present
E. S.	M	28	Second right	Grade 2	None	D 2	Grade 2	None	Present	Absent	Present	Present
L. M.	M	32	Second left	Grade 2-3	Grade 2	D 2	Grade 4	None	Present	Present	Present	Present
I. M.	M	38	Second left	Grade 2-3	None	D 2	Grade 2	None	Present	Present	Present	Present
E. C.	M	41	Apex	Grade 5	Grade 3	D 3	Grade 2	Present	Present	Present	Present	Present
J. D.	F	23	Apex, second left	Grade 2	Grade 1	D 3	Grade 2-3	Grade 1-2	Present	Present	Present	Present
H. O.	F	27	Second left	Grade 3	None	D 5	Grade 2	None	Present	Present	Present	Present
D. R.	F	33	Second left	Grade 2-3	None	D 4	Grade 1-2	None	Present	Present	Present	Present
V. K.	F	47	Second left	Grade 3	None	D 2	Grade 2	Present	Present	Absent	Present	Present

greater intensity than over the precordium, constitute a physical sign of uncomplicated coarctation of the aorta, and that these characteristic murmurs are usually accompanied by systolic, and occasionally also by diastolic murmurs heard anteriorly over the base of the heart.

PHONOCARDIOGRAPHIC OBSERVATIONS

In order to obtain a more accurate analysis of the sounds and murmurs in coarctation of the aorta and to demonstrate graphically inaudible vibrations, our fifteen patients were studied by phonocardiogram. The apparatus used was a Sanborn Tribeam phonocardiograph, with logarithmic and stethoscopic microphones and interchangeable chestpieces.[4,5] The reasons for our choice of this instrument, together with a description of a satisfactory phonocardiographic technique, have been recently presented in a study of basal diastolic murmurs.[6] In the present study we placed the microphone over that part of the patient's back at which the murmur was maximal. (These tracings were most satisfactorily obtained when the patient was lying prone with a pillow under his chest to allow forward movement of the shoulders, so that the scapulae might be more widely separated.) Further tracings were taken with the patient supine and the microphone placed over that part of the base of the heart at which the precordial murmur was maximal. The method of standardization of sound intensity described by Rappaport and Sprague[7] was used in this study.

In the tracings taken from the back, a systolic murmur was recorded in every patient, which was to be expected, because this murmur was in every instance audible. Significant diastolic vibrations* were, however, recorded at the same location, not only in the six patients in whom a diastolic murmur was heard on auscultation, but in every one of the remaining nine patients.

Systolic vibrations were recorded from the base of the heart in all fifteen patients, although in one of these patients no systolic murmur was audible. Significant diastolic vibrations* were recorded from this area not only in the five patients in whom a diastolic murmur was audible but also in five additional patients.

These observations indicate a more frequent occurrence of systolic and diastolic vibrations than is found on auscultation. One reason a diastolic murmur may not be audible, although significant diastolic vibrations are recorded phonocardiographically, is that a loud systolic murmur or second heart sound may produce a fatiguing effect on the human hearing mechanism which persists into early diastole. Another reason is that, since the second heart sound is frequently inaudible over the back, the exact onset of diastole cannot be estimated and a murmur may be interpreted as systolic when it actually persists into early diastole.

As our phonocardiograms reveal, the first and second heart sounds may be recorded from the back, and when this is so they do not show appreciable transmissional delay. We have found, too, that when murmurs are widely con-

*Diastolic vibrations are considered significant if they show a period of maximal or minimal intensity which recurs in a similar location in subsequent cardiac cycles.

ducted over the precordium or into the back, their configuration on phonocardiography is not significantly altered. We have, therefore, 'in' our patients with coarctation of the aorta, contrasted the configuration of the murmurs recorded from the back with that of the murmurs recorded from the precordium.

The murmur present over the dorsal spine in these cases was crescendo-decrescendo in character, starting a short interval after the onset of systole and often continuing into early diastole. In only two of these patients was the systolic murmur over the precordium similar in configuration to that over the dorsal spine. In both of these the murmur was of greater intensity over the back and was probably conducted to the precordium. In five additional patients the systolic murmur recorded from the back was of greater intensity than that obtained from the precordium. In these patients, however, the configuration of the murmur in the precordium was different, indicating that it contained vibrations which were not conducted from the back. Finally, in eight patients the murmur was louder in front and did not resemble the recording from the dorsal spine.

The diastolic vibrations recorded over the dorsal spine were decrescendo in configuration in twelve of the fifteen patients. In these twelve patients the envelope of the combined systolic and diastolic vibrations was fusiform in shape. In the three remaining patients inaudible diastolic vibrations were recorded which were minimal in intensity in early diastole and gradually increased in intensity in later diastole. In only one patient the precordial diastolic vibrations were of the same configuration as those from the back but of lower intensity. In two other patients the diastolic vibrations, while similar in configuration, were of greater intensity over the precordium.

In seven patients diastolic vibrations from the precordium had a crescendo-decrescendo configuration, with maximal intensity shortly after the second heart sound. In six of these, the vibrations also differed from those recorded from the back in that they were of greater intensity than the vibrations in the latter part of systole. The diastolic vibrations in these seven patients resembled in configuration those of the basal diastolic murmur of aortic or pulmonary insufficiency as described by Wells, Rappaport, and Sprague.[6] This would, of course, suggest the additional diagnosis in these cases of a congenital bicuspid aortic valve. Only one of the seven patients has died, but autopsy confirmed this diagnosis in his case, a full description of which has been presented by Clark and Ferminger.[8] In another of the seven patients the diastolic murmur was so characteristic on auscultation that the clinical diagnosis of aortic insufficiency was made. In only one of the remaining five patients were the diastolic vibrations accompanied by an audible diastolic murmur, and their significance remains obscure.

It is interesting to observe that in five of seven patients in whom diastolic vibrations were recorded from the precordium and dorsal spine, these vibrations differed markedly in configuration and were evidently produced by unrelated mechanisms.

PHONOCARDIOGRAMS ILLUSTRATING THESE OBSERVATIONS

The murmur recorded from the dorsal spine in Fig. 1 is characteristic of those found in coarctation of the aorta. The vibrations are crescendo-decrescendo in configuration, continuing into early diastole and becoming minimal before the onset of systole. The very loud murmur recorded over the precordium is slightly different in configuration in that it has a high intensity in early systole.

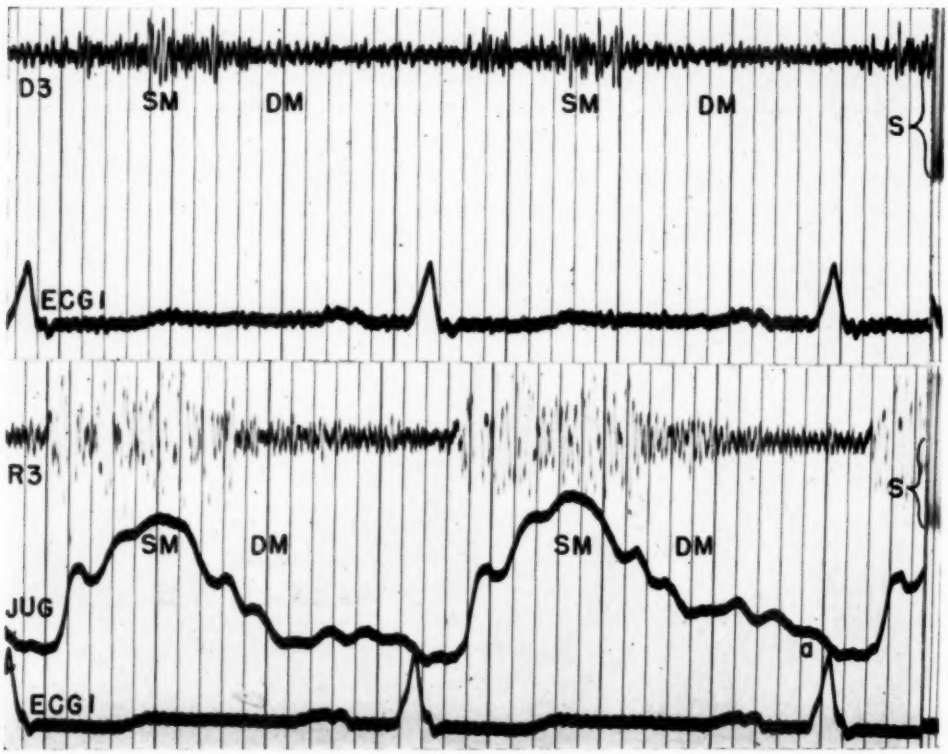

Fig. 1.—E. C., a 41-year-old man. Abnormality of heart discovered at age of 18. Hemoptyses of about 8 fluid ounces four times in last few years; recent dyspnea and palpitation. Grade 4 systolic murmur at apex; Grade 3 at base with Grade 3 diastolic murmur. At back both murmurs were heard, though less well. *D3*, Logarithmic microphone with large open bell over third dorsal spine; *R3*, logarithmic microphone with large open bell over third right intercostal space; *Jug.*, jugular pulse; *Ecg.*, Lead I.

Note the band "S" at the end of each tracing, representing the response of the instrument to a constant sound source of 500 cycles at 80 decibels above the threshold of audibility.

The first and second heart sounds are clearly recorded in the tracing from the dorsal spine in Fig. 2, where they are synchronous with the heart sounds recorded from the precordium. No diastolic murmur was heard in this patient, but the tracings demonstrate that the vibrations of the loud systolic murmur continue into early diastole in most cardiac cycles. The fact that the systolic murmur is of greater intensity over the back than over the precordium can be

demonstrated by relating the amplitude of the vibrations in each instance to that of the standard sound intensity which is shown immediately following each separate recording (see footnote to Fig. 1). This fact, together with the similarity of configuration of the two murmurs, would indicate that the systolic murmur in the back is conducted to the precordium.

Although no diastolic murmur was heard over the dorsal spine of the patient whose tracing is shown in Fig. 3, characteristic vibrations are recorded,

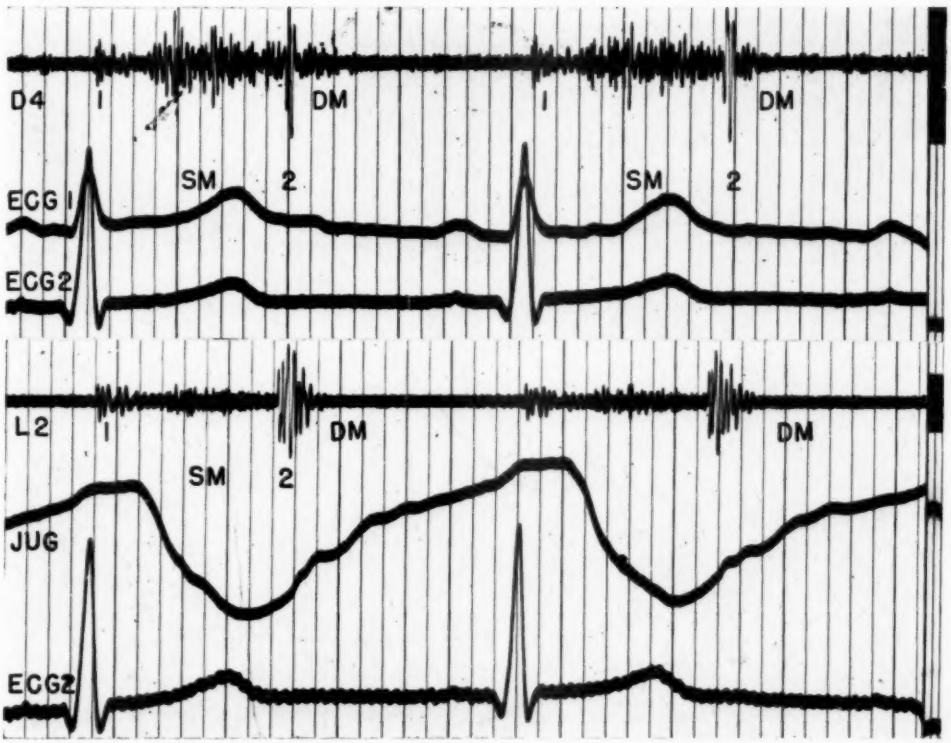

Fig. 2.—J. T., a 9-year-old boy. Abnormality of heart found at age 6. At age 7 blood pressure 152/86. Asymptomatic. Systolic murmur, Grade 3, along left sternal border and Grade 3 to 4 at fourth dorsal spine. No diastolic murmur. *D4*, logarithmic microphone with large open bell at fourth dorsal spine; *L2*, logarithmic microphone with large open bell over second left intercostal space; *Jug.*, jugular pulse; *Ecg.*, Leads I and II.

starting a considerable interval after the onset of systole and extending into early diastole. There is a louder murmur over the precordium, which is slightly shorter in duration and falls off in intensity before the second heart sound. Diastolic vibrations of decrescendo configuration are also recorded from the precordium, although in this location as well no diastolic murmur was audible. The reason that no diastolic murmur was audible in either location is probably that the systolic vibrations and second heart sound are of such intensity as to create a fatiguing effect on the human hearing mechanism which would persist into early diastole.

The characteristic systolic murmur over the dorsal spine, continuing in a decrescendo manner into early diastole, is very well shown in Fig. 4. The precordial tracing shows a systolic murmur of considerably lower intensity and different configuration. The diastolic murmur recorded over the left sternal border is crescendo-decrescendo and conforms to the pattern described in aortic or pulmonary insufficiency.[6] This configuration therefore confirms the clinical impression that aortic insufficiency is present.

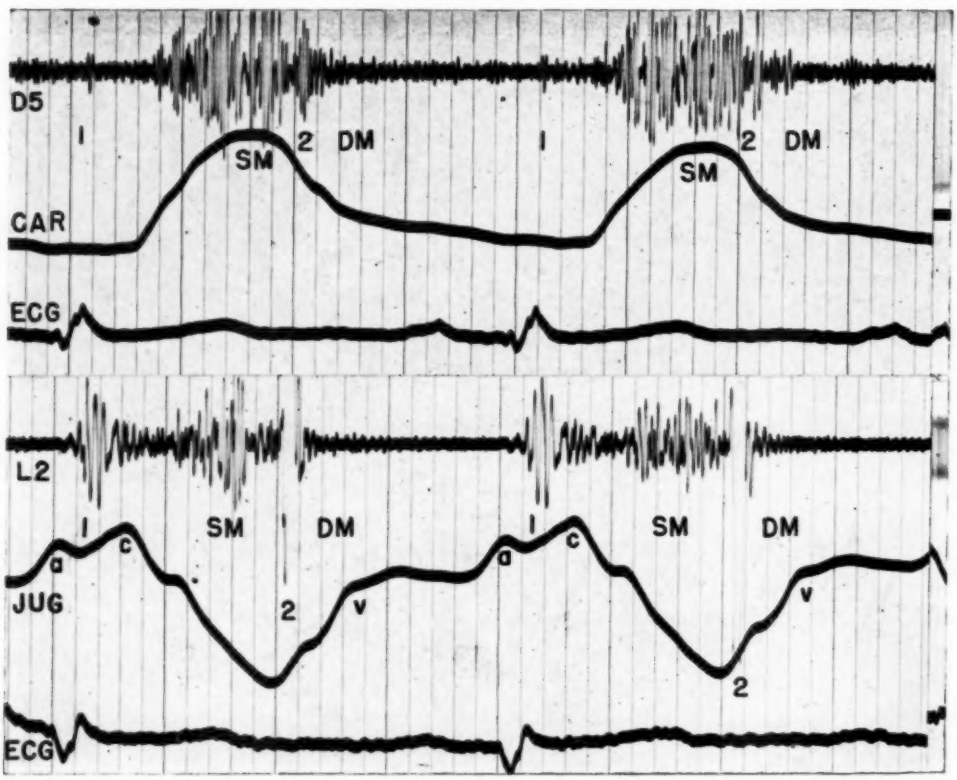

Fig. 3.—H. O., a 27-year-old woman. Congenital heart disease diagnosed at age of 10. Blood pressure 210/130. Systolic murmur, Grade 3, over second left intercostal space; Grade 2 over fifth dorsal spine. No diastolic murmur. *D5*, logarithmic microphone with large open bell over fifth dorsal spine; *L2*, logarithmic microphone with large open bell over second left intercostal space; *Car.*, carotid pulse; *Jug.*, jugular pulse; *Ecg.*, Lead III.

ASYNCHRONISM OF FEMORAL AND RADIAL PULSES

Asynchronism of pulsation of the radial and femoral arteries, which was investigated and described by Lewis[9] in 1933, has not been widely used in recent years as a diagnostic test. Lewis showed that in the normal patient the onset of the upstroke and the summit of the pulse wave are earlier in the femoral than in the radial artery, while in patients with coarctation of the aorta the re-

verse occurs. Synchronous pulse tracings are very easily and satisfactorily recorded on the Sanborn Tribeam phonocardiograph by the use of two of the capsules described by Miller and White.[5,10] Illustrations of tracings taken in a patient with coarctation of the aorta and in a normal control subject are shown in Figs. 5 and 6. We believe that the demonstration of abnormal asynchronism constitutes a test which is of value in the diagnosis of coarctation of the aorta and should be more widely used.

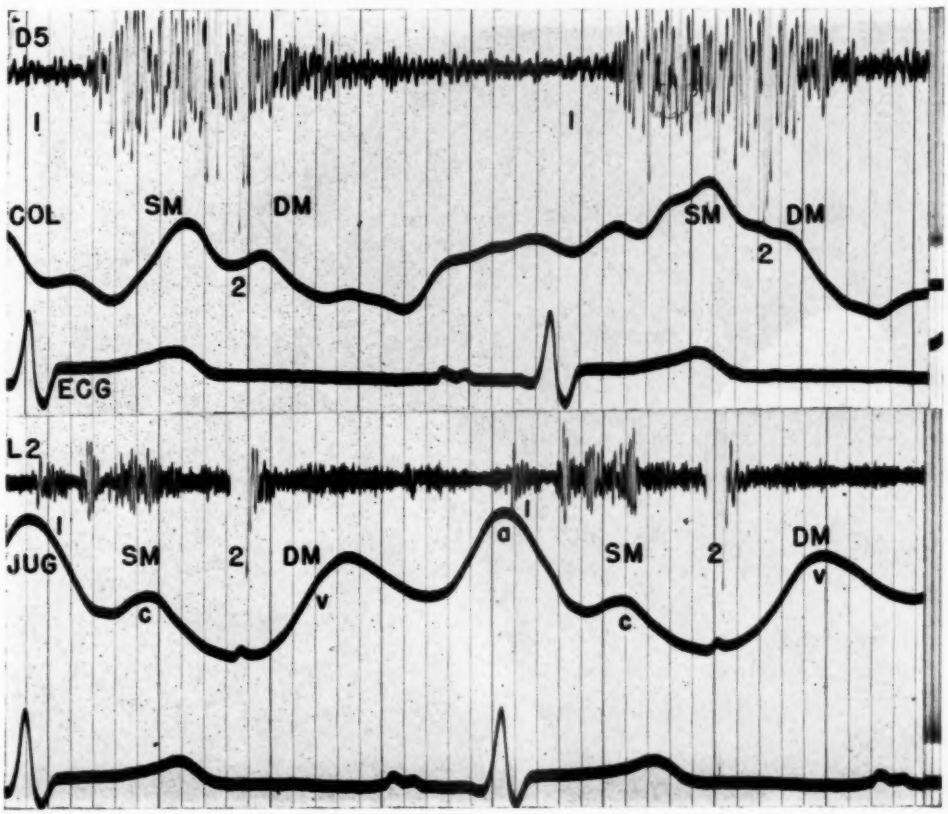

Fig. 4.—J. B., a 22-year-old man. Severe epistaxes over one month; otherwise asymptomatic. Heart enlarged. Grade 2 systolic and Grade 2 blowing diastolic murmurs over second left intercostal space. Grade 3 systolic murmur continuing into diastole at fifth dorsal spine. *D5*, logarithmic microphone with large open bell at fifth dorsal spine; *L2*, logarithmic microphone with Bowles diaphragm (0.015 inch thick) at second left intercostal space; *Col.*, pulse tracing from collateral channel over the back; *Jug.*, jugular pulse; *Ecg.*, Lead II.

SUMMARY AND CONCLUSIONS

1. Opinions differ as to which murmurs are characteristically present in uncomplicated coarctation of the aorta and which are due to concomitant defects.

2. In fifteen patients with coarctation of the aorta a systolic murmur was present over the dorsal spine in every case, and over the precordium in every case but one.

3. A diastolic murmur was present in six of these patients over the dorsal spine, and in five patients over the precordium.

4. Both systolic and diastolic murmurs are occasionally of greater intensity over the dorsal spine than over the precordium. Such a distribution of intensity is never present in the murmurs of isolated aortic value deformity or patency of the ductus arteriosus, and in these fifteen patients there was no instance in which the murmurs were louder over the collateral vessels than over the dorsal

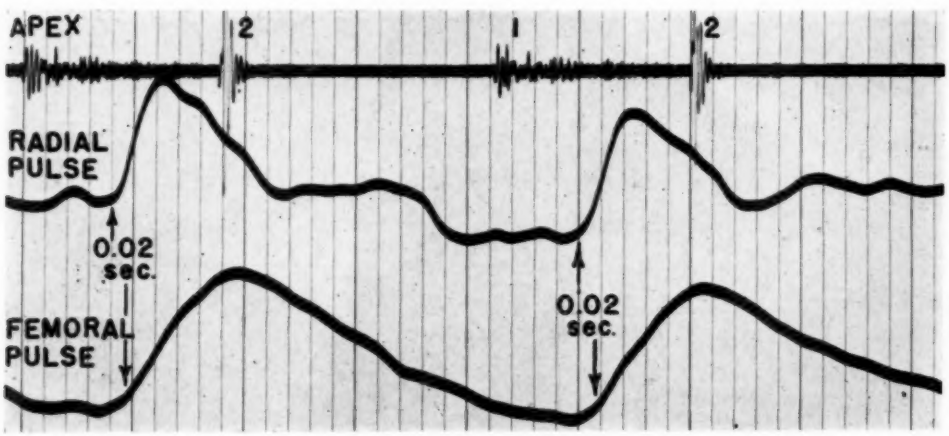

Fig. 5.—Synchronous tracings of femoral and radial pulses together with heart sounds in coarctation of aorta (Patient J. B.). (See also Fig. 4.)

Note that the onset of expansion is later in the femoral artery, which is characteristic of coarctation of aorta.

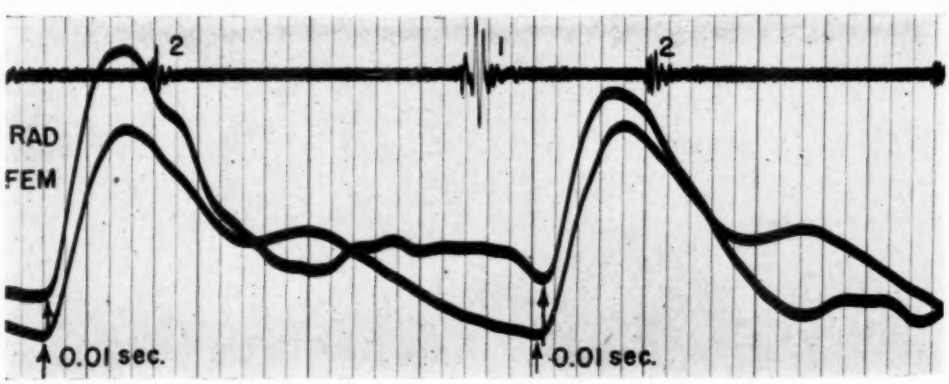

Fig. 6.—Synchronous femoral and radial pulse tracings in normal control subject, showing the femoral pulse preceding the radial pulse by 0.01 second.

spine. It is therefore probable that both systolic and diastolic murmurs are frequently present in uncomplicated coarctation of the aorta.

5. The method of study of the fifteen patients by phonocardiography is described, and the tracings obtained reveal the following facts: (a) Significant diastolic vibrations were present in tracings from the dorsal spine in every patient, although in only six of them was a diastolic murmur heard. The diastolic vibrations were characteristically of descrescendo configuration, being a continuation from the systolic murmur. (b) Diastolic vibrations from the precordium were recorded in ten patients, although a diastolic murmur was heard in only five of these. However, the vibrations were usually of different configuration from those recorded from the dorsal spine and were therefore caused by a different mechanism; in the majority of cases the configuration of these vibrations resembles that found in aortic insufficiency.

6. It is believed that systolic and diastolic vibrations from the dorsal spine are found on phonocardiography even more characteristically than they are heard on auscultation.

7. The reasons that diastolic vibrations may not be audible as a diastolic murmur are: (a) The intensity of a loud systolic murmur may be such as to cause a fatiguing effect on the human hearing mechanism which would mask the murmur in early diastole. (b) The frequent absence of the second heart sound on auscultation over the back may obscure the fact that the murmur extends into early diastole.

8. A satisfactory method for making synchronous records of the radial and femoral pulses is described. It is considered that the registration of abnormal asynchronism constitutes a test which is worthy of wider use in the diagnosis of coarctation of the aorta.

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INTERATRIAL SEPTAL DEFECT

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RECENT developments in the study of congenital heart disease have necessitated a more careful evaluation of clinical material. It is surprising that so few clinical studies of atrial septal defect comparable to that of Bedford, Papp, and Parkinson[1] are available in the literature. Our purpose is to describe the clinical and laboratory features in thirty-five cases of atrial septal defect and to evaluate the various diagnostic procedures at present available in the study of this, the most common lesion in congenital heart disease. The relative value and diagnostic significance of fluoroscopy, circulation times, angiocardiography, and venous catheterization will be discussed.

The material consists of sixteen unselected clinical cases collected during a period of eighteen months in a large cardiovascular clinic. On all patients adequate histories, physical examinations, fluoroscopy, and laboratory tests were available. Four of these cases came to necropsy. Another series of nineteen unselected autopsy cases was used to obtain further information on the pathology of this congenital lesion. In this particular series the clinical information was less detailed and is not included in our study.

HISTORICAL FEATURES

Not until 1934 was any attempt made to collect the available literature in a clinical analysis of cases. Roesler[7] analyzed sixty-two cases, including one of his own. Shortly before this, McGinn and White[3] had discussed the combination of interatrial septal defect and mitral stenosis. In 1938, Taussig, Harvey, and Follis[4] reported four patients who came to necropsy and again emphasized the frequency of superimposed valvular disease, especially mitral stenosis, which in their cases, they considered to be caused by rheumatic fever. Recent interest in angiocardiography has added little to previous fluoroscopic studies. In reviewing ten cases, Steinberg, Grishman, and Sussman[8] were able to supply important diagnostic information in only one case. Of greatest value have been the studies of right heart catheterization, such as those of Brannon, Weens, and Warren[9] and those of Burwell and Dexter.[10] The validity of the results and the diagnostic significance of the procedure will be discussed later. Finally, the

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work of Hitzig[11] with circulation times has added another important contribution to the diagnostic armamentarium.

EMBRYOLOGY AND PATHOLOGY

The embryology and pathology of interatrial septal defect have been discussed by Bedford, Papp, and Parkinson.[1] They feel that (1) the clinical entity of atrial septal defect is a congenital malformation to be distinguished from simple probe patency of the foramen ovale; (2) it is the most frequent of all congenital cardiac malformations, constituting, as a single lesion, 7 to 25 per cent of all such cases; (3) it is almost always located at the fossa ovalis, and is due to defect in closure, involving the septum primum, the septum secondum, or the septum intermedium.

Two hypotheses concerning the dynamics of atrial septal defect might be mentioned. Schnitker,[5] referring to Straub,[6] has stated that left atrial pressure measured in the dog is significantly greater than right atrial pressure (a point in conformity with the mechanism of closure of the foramen ovale at birth) and that this mechanism may account for the left-to-right shunt. Uhley,[12] in refuting this mechanism, believes that the explanation is a simple hydrostatic one, and points to the more cephalad position of the left atrium. This gravitational effect should be considered and is a factor in the Bernouilli equation of energy of flow. Brannon[9] states that "a satisfactory explanation of the left-right shunt has not been offered." His studies with venous catheterization have added significant information to this vexing problem. The apparent pressure difference between the left and right atrium varies from 2.0 to 4.0 millimeters of mercury. The arterial oxygen saturation of the right atrium does not appear to be affected by placing of the patient in the head down position. It would thus appear that the intrinsic difference in pressure between the left and right atria is the more adequate explanation of the left-to-right shunt in uncomplicated atrial septal defect. By cardiac catheterization the output of the right ventricle is found to be approximately twice that of the left ventricle, the left ventricular output being within the normal range. The post-mortem findings in nineteen cases of interatrial septal defect are summarized in Table I.

The findings in Table I conform in general with the previous pathologic concept of the interatrial septal defect. The findings in our series can be summarized as follows:

1. Enlargement of the right side of the heart was predominant.

2. The atrial septal defect was always over 1.0 cm. in diameter and averaged 2.0 to 7.0 centimeters.

3. The pulmonary-vascular system was always affected to some degree, usually with gross dilatation and often with moderate atherosclerosis of the pulmonary vessels.

4. The left side of the heart was often affected, in the absence of complicating lesions such as mitral stenosis or coarctation. When the left side of the heart was enlarged, it occurred along with enlargement of the right side. This

involvement of the left side of the heart is an unusual finding in conjunction with right side enlargement and may represent a situation similar to cor pulmonale; for example, there is very frequent left side involvement in the presence of hypertrophy of the right ventricle.

TABLE I. PATHOLOGIC FINDINGS IN NINETEEN CASES OR INTERATRIAL SEPTAL DEFECT STUDIED POST MORTEM

1.	Average weight of heart	594.2 grams
2.	Right atrium:	
	Mildly dilated	3 patients
	Moderately dilated	4 patients
	Markedly dilated	5 patients
	Unrecorded	7 patients
3.	Left atrium:	
	Mildly dilated	6 patients
	Moderately dilated	3 patients
	Markedly dilated	1 patient
	Normal	1 patient
	Unrecorded	8 patients
4.	Average width of right ventricle	6.2 mm. (17 cases)
5.	Average width of left ventricle	13.0 mm. (14 cases)
6.	Average width of atrial septal defect	2.7 cm. (18 cases)
7.	Average circumference of mitral valve (none with mitral stenosis)	11.2 cm. (14 adults)
8.	Myocardium:	
	Normal	7 patients
	Infarct	4 patients
	Unrecorded	8 patients
9.	Evidence of moderate to marked arteriosclerosis:	5 patients
10.	Average age at death	49 years
11.	Causes of death:	
	Unrecorded	4 patients
	Heart failure	8 patients
	Bacterial endocarditis, coronary embolism, myocardial infarction, cerebral thrombosis, paroxysmal embolus, bronchial pneumonia, infarct with failure (each of these)	1 patient
12.	Complications of atrial septal defect:	
	Coarctation of aorta	2 patients
	Subacute bacterial endocarditis	1 patient

5. Uncomplicated interatrial septal defect allows a life span of many decades. In this series the age average at death is strikingly high. The oldest patients were 78 to 80 years old.

6. The diagnosis of interatrial septal defect often appeared secondary to various types of degenerative heart disease.

CLINICAL FEATURES

Certain unusual aspects of interatrial septal defects distinguish this anomaly from other congenital cardiovascular abnormalities. The most significant of these are listed:

1. Interatrial septal defects appear more frequently in the female than in the male. In Roesler's[7] series of sixty-two cases 61.7 per cent of the patients were female; in the fifty-two cases comprising the series of Bedford and associates,[1] 80 per cent were female; and in our own series 81 per cent of sixteen clinical cases and 58 per cent of nineteen autopsied patients were female. The explanation of this sex linkage is not clear. Medvei and Roesler[15] speak of the hereditary tendency in the pathologic changes in cardiac development. Such marked sex linkage would seem to be more likely "genototypically conditioned," as Medvei and Roesler suggest, than the result of virus disease in the mother.[14]

2. The extreme rarity of subacute bacterial endocarditis has received frequent comment. In our single case the bacterial lesion was not present at the site of the defect. Bedford and his associates[1] state that the literature presents only one case in which the vegetation was present along the septal defect.

3. The absence of significant associated congenital abnormalities is a matter of some importance. Roesler's[1] series showed fifteen patients with associated congenital abnormalities, but only four of these (four cases of coarctation) appeared significant. In the ten autopsied cases in the series of Bedford and co-workers[1] ventricular septal defect was present once, slight coarctation once, and slight patency of the ductus arteriosus once. In our autopsy series, coarctation was present twice; in the clinical series, interventricular septal defect, bicuspid aortic valve with aortic regurgitation, coarctation, and patent ductus arteriosus were each present once.

4. The association of valvular heart disease has been frequently discussed. The mitral valve, involved in thirty of Roesler's[7] sixty-two cases and in four of the ten autopsied cases of the series of Bedford and associates,[1] is the most frequently associated lesion, and is presumably of rheumatic origin. Clinical correlations of heart size, with and without mitral stenosis, tend to minimize the importance of the valvular defect in affecting chamber enlargement. Bedford,[1] stated: "The heart, on the whole, appeared to be more voluminous when mitral stenosis was present." From a purely clinical standpoint, the diagnosis of mitral stenosis is probably made less frequently than the lesion is present, because of the marked cardiac rotation inspired by the huge right ventricle. In our clinical series, a mitral diastolic murmur was heard twice.

PHYSICAL SIGNS

It has been repeatedly emphasized in previous clinical studies that no physical signs in atrial septal defect have real diagnostic significance. We have strongly suspected the diagnosis of atrial septal defect on two occasions prior to fluoroscopy. This has been on the basis of clinical signs alone, without

significant information concerning the presence of heart disease from birth, or other definite leads. We do not wish to imply that the diagnosis can be made without fluoroscopy, and it is certainly to be assumed that the factor of error in such "clinical suspicion" is quite large. The salient feature of this "clinical suspicion" is the evidence of right ventricular enlargement *without* the presence of mitral stenosis or other pathology responsible for right ventricular enlargement.

Our purpose in calling attention to the physical signs of marked right ventricular enlargement is similar to that of Roesler.[7] We feel that it adds materially to the clinical appraisal and helps to differentiate other disease entities, such as primary pulmonary disease and constrictive pericarditis. It is pertinent here to quote Roesler,[7] who has given so much attention to cardiac pulsations: "In enlargement of the right ventricle of considerable degree, but without hypertrophy, pulsatory heaving of the lower sternum occurs . . . . The systolic propulsion of the lower central portion of the thoracic wall is due partly to change in shape of the cardiac mass from a transverse ellipse in cross section to a cone, and partly to recoil. The latter factor is increased by high pressure in the pulmonary artery, and by increased filling of the right ventricle. As long as the left ventricle is not displaced, a normal circumscribed apical thrust may persist. In the presence of considerable enlargement of the right ventricle, the front wall of the heart is mainly formed by it, and so is the apical thrust, the left ventricle having been pushed away from the wall of the chest. This finding of a well-circumscribed resistant thrust in the apical region in the presence of a predominant and enormous right-sided enlargement, is not known for any other clinicopathologic condition than atrial septal defect."

The physical signs, therefore, are the physical signs associated with right ventricular hypertrophy, and are listed in Table II.

Precordial bulge, displacement of the apex beat, mitral and pulmonic murmurs, accentuation of the pulmonic second sounds, and so forth, are all manifestations of isolated right ventricular hypertrophy. The mitral diastolic murmur alone is the physical sign of significance in the differentiation of pure atrial septal defect from Lutembacher's syndrome.

Much controversy has arisen concerning the relationship of heart size to the presence or absence of murmurs. It is certainly true that no murmurs may be present with considerable right-sided enlargement (two of the cases with necropsy proof in the series of Bedford, Papp, and Parkinson[1]). It is also quite definite that small defects, asymptomatic, without evidence of cardiac hypertrophy, and with only a prominent bulge in the region of the pulmonary conus, may constitute a "subclinical" group of patients. Little exact information is available in this group. As a general rule, however, there is some relationship between the loudness of the pulmonic murmurs, the presence of a systolic thrill, and the presence of a pulmonic diastolic murmur to the heart size and general condition of the patient. According to Thompson,[13] a prominent pulmonic systolic murmur is a rather late clinical sign, and the presence of a thrill or diastolic murmur is in general associated with huge defects and considerable

cardiac enlargement. The murmur is due to dynamic factors within the pulmonary artery and not to the atrial septal defect itself.

TABLE II. SYMPTOMS AND SIGNS IN SIXTEEN CLINICAL CASES OF ATRIAL SEPTAL DEFECT (AVERAGE AGE, 23 YEARS)

		Cases
A.	*Symptoms*	
	1. Shortness of breath	9
	2. Palpitations	4
	3. Hemoptysis	4
	4. History of heart failure	3
	5. "Pneumonitis"	3
	6. Substernal pain	2
	7. "Arthritis"	1
B.	*Signs*	
	1. Cyanosis	7
	2. Clubbing	1
	3. Increased second pulmonic sound	6
	4. Pulmonic systolic thrill	2
	5. Pulmonic systolic murmur, marked	4
	Pulmonic systolic murmur, moderate	8
	Pulmonic systolic murmur, mild	2
	Pulmonic systolic murmur, none	2
	6. Pulmonic diastolic murmur	7
	7. Mitral systolic murmur	3
	8. Mitral diastolic murmur	1
	9. Mitral systolic and diastolic murmurs	1
	10. Right heart failure	4

RADIOLOGIC FEATURES

From what has been previously stated, it is apparent that the presumptive diagnosis of atrial septal defect depends upon radiologic diagnosis. The "clinical suspicion" referred to earlier becomes almost a certainty following the adequate demonstration of gross, isolated, right-sided cardiac enlargement, together with large central pulmonary arteries, with or without obvious pulsations. However, the so-called hilar dance, or obvious pulsations of the large pulmonary arteries, aids greatly in establishing a presumptive diagnosis. In no other condition is the evidence of enlargement of the pulmonary arterial bed more dramatic. The characteristic roentgenologic features follow:

I. *In the Anteroposterior Position.*—

A. Enlargement of the heart chiefly to the left, *produced by enlargement of the right ventricle.*

B. Prominence and elongation of the pulmonary arc. This is usually the case with small defects. With large defects, extreme, almost aneurysmal bulging of the pulmonary arc is typical.

C. Enlargement of the heart to the right is unusual. Rarely enlargement to the right may be more pronounced than to the left (six of the cases of Bedford and associates[1]).

D. The right pulmonary artery forms a large, dense, well-defined, almost comma-shaped shadow in the right hilar region. The left pulmonary artery occasionally protrudes beyond the pulmonary arc, forming a double contour.[16]

E. Pulmonary congestion in the periphery and hydrothorax is conspicuous by its absence, even in the presence of congestive failure. Quite typical is the contrast between the radiant peripheral lung fields and the dense agglomeration of hilar shadows.

F. Pulsation of the hilar pulmonary arteries is often seen (hilar dance). We have found this more definite and frequent in the right hilar region, presumably because of the ease with which the vessels near to the heart are seen.

II. *In the Right Oblique Position.*—

A. Enlarged pulmonary conus and pulmonary artery. There is increased width of the heart shadow in its upper one-third.

B. Visualization of the right pulmonary artery as an oval pulsating mass in front of the aorta, and just above the right bronchus. This is seen so easily since its density is due to the "end on" view of the right pulmonary artery. It is the "pulmonal fleck" as described by Schwedel and Epstein.[2]

C. Posterior displacement of the esophagus by the enlarged pulmonary vessels.

D. Occasional budge in the region of the left atrium. In the series of Bedford and associates,[1] four showed slight left atrial enlargement fluoroscopically, and of these only one patient had clinical mitral stenosis.

III. *In the Left Oblique Position.*—

A. The position of the left branch of the pulmonary artery, crossing and obscuring the pulmonary window, is important.

B. The left ventricle is of normal size. The right ventricle may present a prominent bulge or "auricular shelf."

A summary of the x-ray findings in twelve of our clinical cases is shown in Table III.

CIRCULATION TIMES

A presumptive diagnosis of atrial septal defect, such as that afforded by the typical fluoroscopic picture, is not entirely satisfying. The picture may be simulated by primary pulmonary hyperplasia, by rare cases of thyrotoxicosis, or by the tetralogy of Eisenmenger. The proof of an intracardiac shunt should be secured. A method of achieving this aim is by the use of circulation times, as recently reviewed by Hitzig.[11] The short-circuiting of ether from right to left, without its passing through the lungs, caused peculiar paresthesiae in the face,

TABLE III. X-RAY FINDINGS IN TWELVE CLINICAL CASES OF ATRIAL SEPTAL DEFECT

1.	Cardiac enlargement:		10 (Recorded)
	Slight	6	
	Moderate	2	
	Marked	2	
	Predominant enlargement to left	8	
	Enlargement *to right and to left*	2	
2.	Pulmonary conus abnormal:		12
	Markedly enlarged	8	
	Moderately enlarged	2	
	Slightly enlarged	2	
	Hilar dance	7 (of 12)	
3.	Pulsating right pulmonary artery in right oblique position		3

arms, and legs, which is often wavelike in character. In atrial septal defect it has been shown that the arm-to-lung ether time and the arm-to-face ether time (paresthesia) are similar. The Decholin or saccharin times are not disturbed, except in the presence of mitral stenosis. The following times are taken from Hitzig[11] to illustrate this point:

	SACCHARIN (ARM-TO-TONGUE)	(ETHER ARM-TO-FACE)	ETHER (ARM-TO-LUNG)
Interatrial septal defect	17.5	8.0	8.5
Lutembacher's syndrome	22.0	8.5	8.5

The ability of circulation times to rule out interatrial septal defect has not yet been clinically confirmed. When the test is positive, it adds greatly to the strength of the diagnosis. In all probability, a negative result is not of great significance.

CARDIAC ANGIOGRAPHY

Of little value is cardiac angiography. Steinberg, Grishman, and Sussman[8] were able to demonstrate the defect only once in ten attempts. It should be shown that the left atrium becomes opaque at the time of right atrial filling. It is apparent that this can be accomplished only when there is a temporary and artificial reversal of flow, and the Diodrast is directed into the heart under pressure. As mentioned by these authors, revisualization of the right atrium following filling of the left heart chambers would probably be quite inconclusive, as a result of the marked dilution which would occur.

CARDIAC CATHETERIZATION

The most reliable diagnosis of interatrial septal defect is achieved by the cardiac catheter.[9] Positive proof of the interatrial septal defect may be secured by passing the catheter from the right atrium into the left atrium. Any septal

defect sufficiently large to permit passage of the catheter would probably represent a clinically significant interatrial septal defect. This procedure has been accomplished by Brannon, Weens, and Warren[9] in one case and by ourselves in one case. The position of the catheter in the left atrium is confirmed by the obtaining of fully oxygenated blood, the oxygen content of which is similar to that of femoral artery blood. To increase the certainty of the diagnosis, pressure tracings in this position should conform to routine atrial pressure curves. If one is unable to pass the catheter into the left atrium, a presumptive diagnosis of interatrial septal defect may be made by showing a definite increase in the oxygen content of the blood of the right atrium over that of the blood of the superior vena cava. According to Burwell and Dexter,[10] the greatest normal variation in the blood oxygen content between the superior vena cava and the right atrium is 1.9 volumes per cent. In the three cases reported by Brannon, Weens, and Warren,[9] the oxygen content of the blood from the right atrium averaged 14.2 volumes per cent, with an average of 11.3 volumes per cent and 11.6 volumes per cent for blood from the superior vena cava and inferior vena cava, respectively. Thus, if the oxygen content of the blood from the right atrium is 2 or more volumes per cent greater than that from the superior vena cava, a presumptive diagnosis of interatrial septal defect may be made; the diagnosis is presumptive because anomalous pulmonary veins emptying into the right atrium could cause a similar result. To our knowledge, catheterization of the pulmonary veins entering in either the right or left atrium has not thus far been accomplished.*

In summary, the most positive diagnosis of interatrial septal defect is made by (1) the passage of the catheter from the right into the left atrium, (2) the withdrawal of fully oxygenated blood in this position, (3) the simultaneous recording of pressure curves from right and left atria with a double lumen catheter. These curves should fit the routine atrial pattern, but left atrial pressure will be appreciably higher than right. The presumptive diagnosis of interatrial septal defect is made by the finding of increased oxygenation of right atrial blood. The oxygen content of the right atrial blood should be 2 volumes per cent or more than that of the superior vena cava.

CONCLUSIONS

1. An analysis has been made of thirty-five cases of interatrial septal defect. Sixteen were studied clinically and nineteen post mortem. Autopsy confirmation was secured in four of the cases studied clinically.

2. The diagnostic criteria of interatrial septal defect have been analyzed and the following general statements may be made:

A. The symptomatology in interatrial septal defect is not distinctive, the most common presenting complaints being fatigue and shortness of breath.

B. Physical examination may point to the presence of right ventricular hypertrophy, which in the absence of mitral stenosis, particularly in a young individual, is suggestive of interatrial septal defect.

*The authors have found the catheter in transposed pulmonary veins entering the right atrium in a case of tricuspid atresia.

C. Adequate fluoroscopy should demonstrate right ventricular hypertrophy and pulmonary hypertension, and should eliminate most conditions to be considered in the differential diagnosis. Abnormal and uniform enlargement of the large pulmonary arterial trunks with or without hilar dance is a necessary feature of the fluoroscopic pattern. Even after adequate fluoroscopy, however, certain conditions such as pulmonary hyperplasia, high ventricular septal defect with gross enlargement of the pulmonary artery, or Eisenmenger's complex, may simulate interatrial septal defect.

D. Circulation times occasionally are of value in showing the presence of a right-to-left shunt.

E. Angiocardiography is of little if any value in the diagnosis.

F. Cardiac catheterization may give information of much diagnostic value. A presumptive diagnosis of interatrial septal defect is established by the finding of increased oxygenation of right atrial blood. A positive diagnosis of interatrial septal defect is made by the passage of the catheter through the septal defect. Confirmation of its position in the left atrium may be obtained by fluoroscopy and film and by the withdrawal of fully oxygenated blood, along with the simultaneous registration of a typical atrial pressure curve.

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RELATIONSHIP BETWEEN THE REDUCTION IN CORONARY FLOW AND THE APPEARANCE OF ELECTRO-CARDIOGRAPHIC CHANGES

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ALTERATIONS of the electrocardiogram characterized by displacement of the RS-T segment and modification in the shape of the T wave were first ascribed to myocardial infarction by Pardee.[1] Subsequent experimental work[2,3,4] showed that electrocardiographic changes of the same type can be reproduced in the dog by complete occlusion of a coronary artery of very brief duration and that such changes disappear immediately after release of the occlusion. Since all previous investigations have been limited to the effect of the complete occlusion of a coronary artery, it consequently seemed of interest to study the relationship between the reduction of coronary flow produced by partial occlusion of a coronary artery and the appearance of electrocardiographic changes.

METHOD

Eleven dogs weighing from 12 to 23 kilograms were used. They were given subcutaneously 2.0 c.c. of a 2 per cent solution of morphine sulfate. Then they received intravenously 1.25 c.c. to 1.5 c.c. per kilogram of body weight of a 20 per cent solution of sodium barbital. Under artificial respiration, the chest was opened through a midsternal incision and the heart suspended in a pericardial cradle. The blood was rendered incoagulable by the intravenous administration of an initial dose of 5.0 mg. of heparin per kilogram, then 3.0 mg. per kilogram every half hour. A segment of the left anterior descending coronary artery was dissected. A cannula was introduced into the distal segment and the distal end of the proximal segment closed (Fig. 1). The mean coronary blood flow was measured and recorded with an electromagnetic rotameter.[5,6] A cannula was inserted in the left common carotid artery; in some experiments, it was introduced down to the root of the aorta in the neighborhood of the coronary ostia. As shown in Fig. 1, when the screw clamps placed in *E* and *G* were open and the screw clamp placed in *F* was closed, the blood was allowed to flow via the carotid cannula (*A*) through the flowmeter (*B*) into the cannulated coronary artery (*C*). When the screw clamps *E* and *G* were closed and the clamp *F* was open, the blood flowed from the carotid cannula (*A*) via the short circuit into the

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cannulated coronary artery (*C*). In this manner, a zero flow was recorded without producing myocardial ischemia. The screw clamp in *E* was also used to reduce temporarily the coronary flow to the desired level. An optical manometer of the Gregg type (*D*) was used to record the mean arterial blood pressure. The flowmeter had been previously calibrated, according to the technique of Shipley and Crittenden,[5,6] with liquids of viscosities covering the range of viscosities of the dog blood in such acute experiments. Numerous determinations of the viscosity of the blood were done during each experiment. Unipolar electrocardiograms were recorded. The indifferent electrode made of German silver was placed under the skin of the dog's left leg and the exploring electrode in the center of the area irrigated via the cannulated coronary artery. The exploring electrode, a nonpolarizable silver-silver chloride electrode, was placed directly on the epicardium, or hooked under the epicardium, or, as in most experiments, hooked in a gauze pad applied on the epicardium and impregnated with physiologic saline solution. Blood pressure and coronary blood flow were recorded continuously throughout the experiments. After one and generally several electrocardiograms were recorded, the blood flow of the coronary artery was reduced to the desired level by means of the screw clamp, *E* (Fig. 1) and maintained at that level by adjustment of the clamp. During and after the occlusion, electrocardiographic tracings were recorded at one-half to one-minute

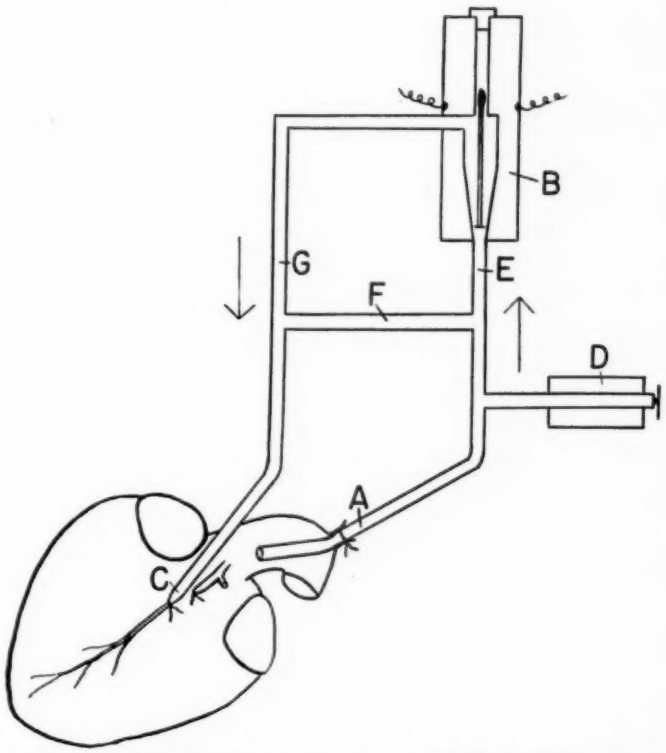

Fig. 1.—Schema of the apparatus used to measure and record the mean arterial blood pressure in the aorta and the mean coronary blood flow in the left anterior descending coronary artery.

intervals. The occlusion was maintained for five minutes in most experiments; in a few experiments, the occlusion lasted three, ten, and fifteen minutes (Table I). In most dogs, several partial or complete occlusions were performed. A period of recovery was always allowed between two successive occlusions.

TABLE I. SUMMARY OF EXPERIMENTS PERFORMED

NUMBER OF EXPERIMENT	DIMINUTION OF CORONARY FLOW (PER CENT)	DURATION OF OCCLUSION (MINUTES)	T-WAVE CHANGE	RS-T SEGMENT CHANGE	DOG
1	10	5	None	None	A
2	10	5	None	None	D
3	12	5	None	None	C
4	17	15	None	None	E
5	18	5	None	None	D
6	20	10	None	None	F
7	23	5	None	None	F
8	25	5	None	None	C
9	25	10	None	None	E
10	29	5	None	None	B
11	29	5	None	None	D
12	29	5	Slight	Slight	D
13	31	5	None	None	G
14	33	5	None	None	E
15	36	5	None	None	I
16	36	5	None	None	K
17	37	5	Slight	Slight	A
18	37	5	Marked	Slight	D
19	42	5	None	None	E
20	43	5	Slight	Slight	C
21	44	5	Slight	None	F
22	44	5	Slight	Slight	H
23	45	5	Slight	None	C
24	48	5	None	None	G
25	49	5	Slight	None	G
26	50	5	Slight	Slight	C
27	50	5	Marked	Slight	C
28	50	5	Marked	Marked	A
29	52	5	Slight	Slight	J
30	56	5	None	None	K
31	57	5	Slight	Slight	K
32	58	5	Slight	None	I
33	58	5	Marked	Marked	D
34	60	5	Slight	None	H
35	61	5	Marked	Slight	E
36	67	5	Marked	Marked	H
37	69	5	Slight	None	I
38	71	5	Marked	Marked	D
39	78	5	Marked	Marked	H
40	79	5	Marked	Marked	G
41	80	5	Marked	Marked	G
42	82	5	Marked	Marked	G
43	85	5	Marked	Marked	K
44	86	5	Marked	Marked	K
45	88	5	Marked	Marked	I
46	89	5	Marked	Marked	I
47	100	3	Marked	Marked	D
48	100	3	Marked	Marked	E
49	100	5	Marked	Marked	G
50	100	5	Marked	Marked	H
51	100	3	Marked	Marked	J

RESULTS

Fig. 2 shows the records of mean arterial blood pressure and flow through the cannulated coronary artery during a typical experiment. During the control period, the mean coronary blood flow ranged between 25 and 18 c.c. per minute and the mean arterial blood pressure oscillated between 120 and 105 mm. of mercury. At the first arrow, the flow through the cannulated coronary artery was reduced by means of the screw clamp. It varied between 11.0 and 8.5 c.c. per minute for five minutes. The blood pressure did not change. At the second arrow, the screw clamp was released. The blood pressure did not change, but the coronary flow rose to a maximum of 39 c.c. per minute, a level higher than the control value, then decreased progressively toward the control value. Such an increase of coronary flow without any change in blood pressure after a partial coronary occlusion has been described previously after temporary complete coronary occlusion.[7] It may be pointed out that such a secondary rise in coronary flow was often observed in our series of experiments after a partial coronary occlusion that was not marked enough to produce any electrocardiographic change.

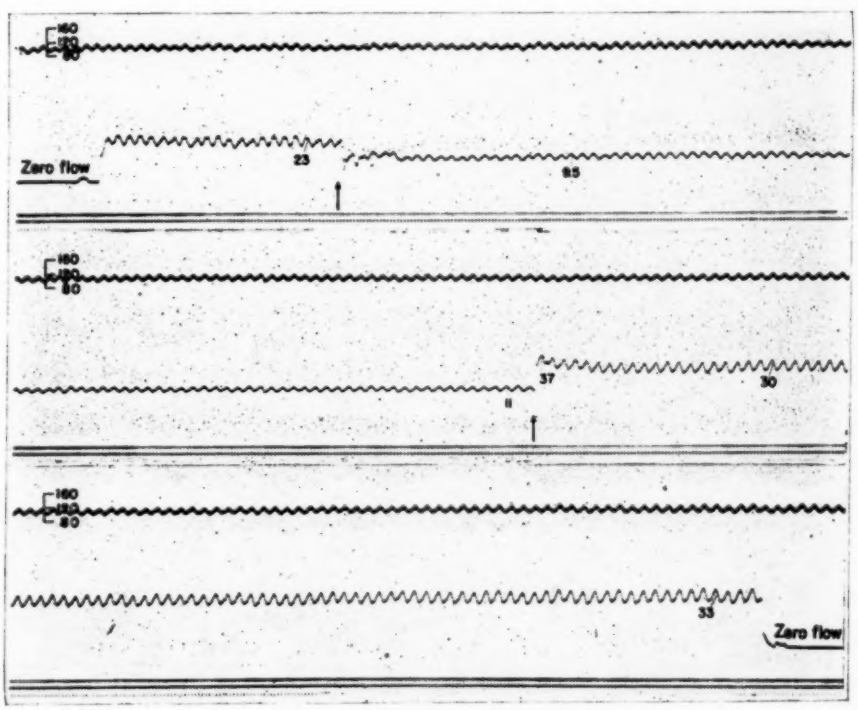

Fig. 2.—Continuous record of the mean arterial blood pressure (upper tracing) and mean coronary blood flow (lower tracing) in a typical experiment.

Scale for the blood pressure in millimeters of mercury. Values for the coronary blood flow in cubic centimeters per minute. At first arrow, partial occlusion initiated; at second arrow, occlusion released. Time in seconds.

Fig. 3 illustrates the electrocardiographic changes observed during a temporary partial occlusion. Tracing *A* is a normal electrocardiogram. In our experiments the T wave of the control electrocardiogram was always inverted. Tracing *B* is the tracing recorded after two minutes of a partial occlusion during which the blood flow was reduced by 78 per cent of its control value (from a control value of 9.0 c.c. per minute to 2.0 c.c. per minute). As can be seen, the T wave is less deeply inverted and the RS-T segment is elevated. Changes of the RS-T segment and T wave of such a degree were termed "slight." Tracing *C* was recorded after three minutes of occlusion. The RS-T segment is more elevated and the T wave less deeply inverted. Changes of the RS-T segment and T wave of such a magnitude were termed "marked." The electrocardiogram was the same after five minutes of occlusion. It must be added that the changes were not sudden but progressive. Tracing *C* also shows a marked degree of electrical alternation, a phenomenon not constantly but frequently observed in our experiments. After the release of the occlusion, the electrocardiographic changes disappeared progressively and the electrocardiogram became entirely similar to the control tracing after four minutes.

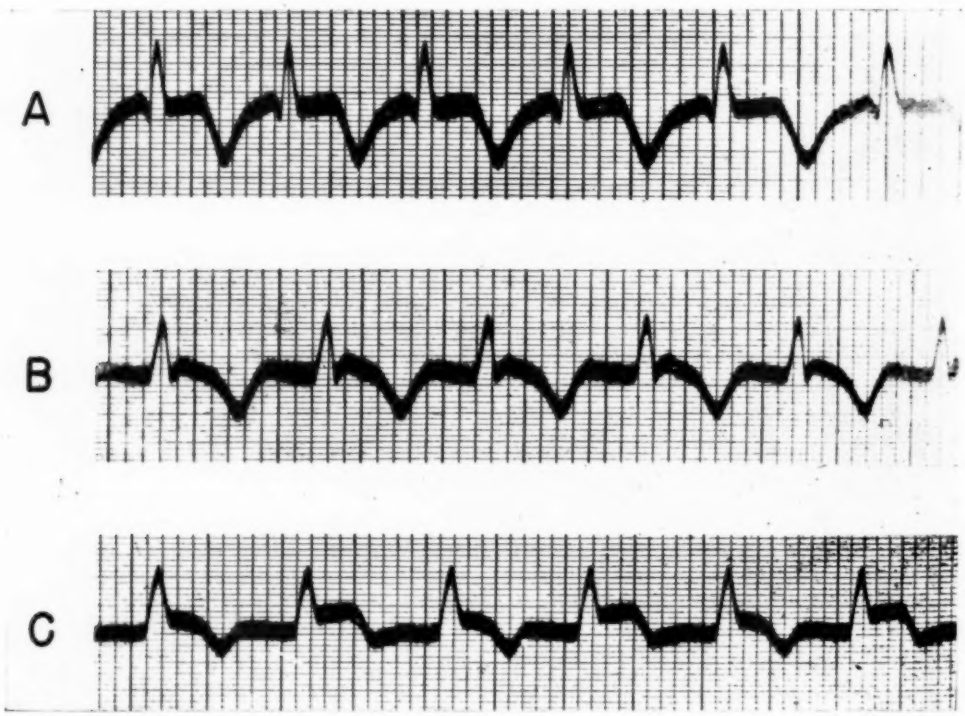

Fig. 3.—Unipolar electrocardiogram recorded from the region of the left ventricle irrigated via the cannulated coronary artery. *A*, Before the occlusion. *B*, After two minutes of partial occlusion during which the blood flow was reduced by 78 per cent of its control value (from 9.0 c.c. per minute to 2.0 c.c. per minute). *C*, After three minutes of the same occlusion. Tracing *B* illustrates changes of the RS-T segment and T wave that are called "slight changes" and *C* illustrates "marked changes" of the RS-T segment and T wave.

As seen in Table I, fifty-one transient partial or complete occlusions of the anterior descending coronary artery were produced in eleven dogs.

In sixteen partial occlusions on nine different dogs in which the blood flow was reduced from 10 to 36 per cent of its control value for a duration of five minutes, no electrocardiographic changes were observed except in Experiment 12, in which there was a slight change in the RS-T segment and T wave. In Experiments 4, 6, and 9, no electrocardiographic changes were observed, although the occlusions lasted fifteen, ten, and ten minutes, respectively.

In twenty-one partial occlusions on ten different dogs in which the reduction in coronary flow amounted to from 37 to 69 per cent of the original flow and was maintained for five minutes, the electrocardiographic changes were variable. Only occasionally was there no change (Experiments 19 and 30). Occasionally there was marked change in both the RS-T segment and T wave (Experiments 28, 33, and 36). In most occlusions, the changes in both the RS-T segment and T wave were slight.

In eleven occlusions on five different dogs in which the coronary blood flow was reduced by 71 to 100 per cent of its control value for a duration of five minutes, the changes in both the RS-T segment and T wave were always marked. The same held true in three more complete occlusions (Experiments 47, 48, and 51) in three dogs which lasted only three minutes.

When the occlusion led to electrocardiographic changes, minimal changes first appeared within about one minute of occlusion and became progressively more pronounced. The changes reached a maximum within three to five minutes of occlusion. Whether more prolonged occlusions would have increased further the degree of electrocardiographic changes was not determined. It seemed that the first change to appear after occlusion was the T-wave change. However, one must remember that T-wave changes are more easily noticed and measured because they are greater than the changes in the RS-T segment, and, therefore, such an observation may be more apparent than real. In all the occlusions done while the dog was in good condition, as gauged by the blood pressure and the coronary blood flow, the electrocardiographic changes produced by partial or complete occlusions of five minutes' duration were completely reversible. The electrocardiographic changes disappeared within three to five minutes after the termination of the occlusion. Under the experimental conditions described, coronary occlusion did not modify the mean arterial blood pressure.

After the release of partial as well as complete occlusion, the coronary flow increased above its control value. This increase was seen to occur even after occlusions that were too slight to produce electrocardiographic changes. It was also observed that the electrocardiographic changes often disappeared before the coronary flow had reverted to its control level.

CONCLUSIONS

An attempt was made to correlate the reduction of coronary blood flow and the appearance of electrocardiographic changes in anesthetized dogs by

measuring the experimentally produced changes in blood flow through a cannulated coronary artery and recording simultaneously the electrocardiogram from the ischemic area of the ventricular myocardium.

A reduction of blood flow of 10 to 35 per cent did not, as a rule, produce any electrocardiographic changes. With a reduction of 35 to 70 per cent, generally "slight" electrocardiographic changes in both the RS-T segment and T wave appeared. Occasionally no change was seen and sometimes the RS-T segment and T-wave changes were marked. With a reduction of 70 to 100 per cent, the changes were always marked.

When electrocardiographic changes were produced by the occlusion, minimal changes appeared within about one minute. These increased progressively in intensity and reached their maximum within three to five minutes. These electrocardiographic changes were reversible and disappeared completely within three to five minutes after release of the occlusion. The effect of longer periods of occlusion was not studied.

A partial occlusion may be too slight to produce electrocardiographic changes, although it may be sufficiently marked to lead to myocardial ischemia as it is shown by the increase of the flow through the cannulated coronary artery above its control value following the release of the occlusion. The electrocardiographic changes generally disappeared before the coronary blood flow had reverted to its control value.

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OBSERVATIONS ON THE POTENTIAL VARIATIONS OF THE CAVITIES OF THE RIGHT SIDE OF THE HUMAN HEART

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IN 1934 Wilson, Johnston, and Hill[1] published observations on the potential variations of the ventricular cavities of the dog's heart and emphasized the bearing of their observations upon the interpretation of the QRS deflections of unipolar epicardial leads. The methods described and the principles laid down in their article were used later in the analysis of the precordial electrocardiogram[2] and have placed electrocardiographic interpretation upon a sounder and more logical basis. With the introduction of catheterization[3] of the human heart it became possible to duplicate many of the observations made in the animal experiments referred to, and also to record the potential variations of the right auricular and right ventricular cavities in various types of cardiac abnormality which do not occur spontaneously in animals and cannot be simulated in experiments.

The first report dealing with intracavitary potential variations in man was made by Hecht[4] in 1946. He concluded that the principles based on animal experiments could be applied safely to the interpretation of the human electrocardiogram. In the following year Battro and Bidoggia[5] studied twelve normal subjects and eleven patients with cardiac abnormalities. They pointed out the resemblance of the tracings obtained from the cavity of the right auricle to those recorded from the auricular levels of the esophagus. In their normal subjects, leads from the right ventricle displayed a small initial R wave, followed by a large S and a negative T deflection. In a case of right bundle branch block the cavity of the right ventricle was initially positive, whereas in one of left bundle branch block it was negative throughout the QRS interval. Shortly after this report appeared, Sodi-Pallares and associates[6] published similar observations on six normal subjects, on twenty patients with heart disease, and on dogs studied under various experimental conditions. They found a great similarity between the records obtained in human bundle branch block and those obtained in dogs in which right or left bundle branch block had been produced experimentally. In their normal subjects, leads from the right ventricular cavity yielded curves similar to those described by other workers. With respect to the ventricular

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complexes of these leads, patients with right ventricular hypertrophy did not differ significantly from normal subjects; those with left ventricular hypertrophy differed only in that the direction of the T wave was upward.

The purpose of our own studies has been to confirm and extend the observations published by others, and in particular to compare the potential variations of the cavity of the right ventricle with those of the right side of the precordium in various types of heart disease.

METHODS AND MATERIAL

We are reporting here only those cases in which it was possible to obtain leads from the cavity of the right auricle and a lead from at least one point in the cavity of the right ventricle.

The fifteen patients studied have been divided into four groups. *Group A* contains six patients with pulmonary stenosis with or without the other features of the tetralogy of Fallot. These patients were cyanotic and all presented evidence of pronounced right ventricular enlargement. *Group B* consists of three patients with essential hypertension and varying degrees of left ventricular enlargement. *Group C* is made up of two hypertensive patients with right bundle branch block. The remaining patients, constituting *Group D*, did not display abnormal preponderance of either ventricle. One had a patent ductus arteriosus; one had had a pericardiectomy for constrictive pericarditis; and two were normal.

All intracavitary electrocardiograms were recorded simultaneously with Lead V_1 by means of a Sanborn Tri-beam Electrocardiograph. Most of the intra-auricular tracings were taken with this instrument operating at the standard sensitivity; in the majority of the intraventricular tracings a deflection of 1.0 cm. represents a potential difference of 3.0 millivolts.

In most instances the electrocardiographic observations were supplemented by measurements of the intracavitary pressures and of the oxygen content of the blood in the chambers on the right side of the heart. In the early cases the catheters used were of the type in which a small wire, terminating in an electrode, is embedded in the catheter wall. Catheters of this kind were found to have two disadvantages: the wire incorporated in the wall reduces the size of the lumen, which makes the withdrawal of blood samples difficult, and by decreasing the flexibility of the catheter, makes its introduction into the right ventricle and the pulmonary artery more difficult.

We, therefore, adopted the following technique. An ordinary 8F or 9F Cournand-type single lumen catheter was first advanced as far as desired. A wire stylet* of spring steel was then advanced through the catheter until its end was within two to three inches of the orifice. The wire was led out of the proximal end of the catheter through a hole bored near the outlet of a standard three-way stopcock, and connected to the electrocardiograph. Inasmuch as the stylet

*The stylets used were supplied by the United States Catheter and Instrument Co. for use with the Cournand catheter. They were of stainless steel, 0.016 inch in diameter, and the end was previously heated to form a small bead and thus prevent injury to the inner surface of the catheter during the insertion of the wire. Before each use the stylet was examined and tested carefully for possible flaws, to guard against the possibility of breakage during the process of insertion.

entered beyond the valve in the stopcock, it was possible to record pressures, to draw samples, or to maintain the infusion without altering the position of the recording wire within the catheter. When electrocardiographic tracings were taken, valuable information as to the location of the catheter tip could be obtained by recording the pressure at its orifice or by obtaining a sample of blood. The presence of the wire within the lumen of the catheter did not appear to alter significantly the pressure tracings taken with a Hamilton manometer, nor did it induce thrombus formation during the withdrawal of blood samples. As a precaution against the latter complication, a high, local concentration of heparin within the catheter was insured, not only by the addition of ten units of heparin per liter to the infusion fluid, but also by the preliminary injection of a stronger concentration of heparin solution just prior to the blood sampling.

Although the distal end of the stylet was never at the end of the catheter, and in a few instances could not be advanced to a point less than four or five inches from it, the potential variations recorded were clearly those taking place at the catheter orifice, for the catheter was a nonconductor. The effect of increasing the distance from the distal end of the stylet to the tip of the catheter was examined and it was found that as this distance became larger the resistance in the electrocardiographic circuit rapidly increased. As this resistance rose, the tracing recorded showed increasing distortion due to stray sixty-cycle current. The general outline of the electrocardiographic deflections was not altered in other respects, even in instances in which the distance from the distal end of the stylet to the catheter tip was increased to as much as three feet. At this distance, however, the voltage of these deflections was only about one-half as great as when the end of the stylet was only a few inches from the orifice of the catheter (Fig. 1).

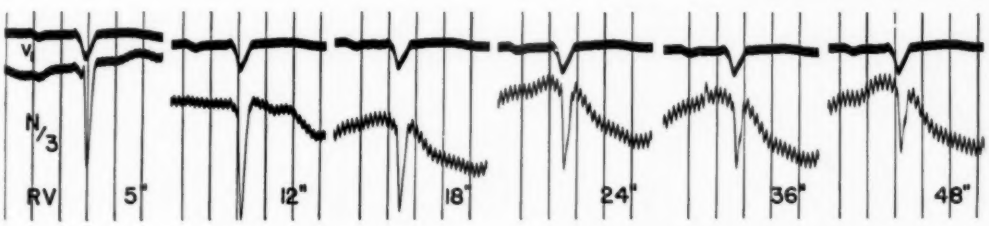

Fig. 1.—Normal subject. Upper beam, Lead V_1. Lower beam, lead from the right ventricle taken with the electrocardiograph at normal sensitivity. The number at the right lower corner of each strip gives the distance in inches of the electrode tip from the intraventricular opening of the catheter.

The suitability, for our purpose, of wires made of various metals was examined by testing them in saline solutions. Although these tests showed that some metals gave larger polarization effects than others, there was no significant difference between the electrocardiograms obtained with different types of electrodes.*

*The authors are indebted to Professor Alfred L. Ferguson, Department of Chemistry, University of Michigan, for his valuable assistance in these problems.

Although the position of the catheter orifice could usually be ascertained by fluoroscopy, pressure readings were relied upon to determine without question that the catheter tip had entered or had been withdrawn from the right ventricle or pulmonary artery. An attempt was made to obtain records from at least three positions within the right ventricle. *Position I* is defined as that in which the catheter tip has just entered the right ventricle from the auricle and lies on the ventricular side of the tricuspid valve. The catheter orifice can be brought into this position by being advanced slowly until the smaller pressure variations characteristic of the right auricular cavity are replaced by the larger pressure variations characteristic of that of the right ventricle. *Position III* is that occupied by the catheter tip when it has been withdrawn from the pulmonary artery and lies on the ventricular side of the pulmonary valve. This position can be identified by the taking of a continuous pressure tracing as the catheter tip is being withdrawn after fluoroscopy has demonstrated its entrance into the pulmonary artery or one of its branches. The arrival of the catheter tip at the desired point is recognized by the sudden transition from the pulse pressures characteristic of the pulmonary artery to the larger pressure variations dependent upon the low diastolic pressures in the right ventricle. *Position II* is that occupied by the catheter tip when fluoroscopy shows that it lies near the cardiac apex and the pressure readings are those characteristic of the right ventricle. It was not always possible to obtain recordings from each of the three positions specified; for, in some instances, the catheter could not, for one reason or another, be advanced to the cardiac apex, or could not be introduced into the pulmonary artery.

In each case leads were taken from three positions in the right auricle. These were determined fluoroscopically and were called *high*, *mid*, and *low*. In the first of these, the catheter tip had just entered the right auricle from the superior vena cava; in the third, it was on the auricular side of the tricuspid valve; and in the second, it was approximately midway between the first and the third. Tracings were occasionally obtained from the superior vena cava and from points within the pulmonary artery. In addition, sometimes the catheter was advanced into the inferior vena cava and from there into branches of the hepatic vein, for the purpose of obtaining semidirect leads from the adjacent parts of the epicardial surface of the right or left ventricle (Fig. 5). Our experience with these last leads is limited, but it is felt that they may be of some value.

The intervals from the beginning of the QRS interval to the peak of the R wave and to the nadir of the S wave were measured* to the nearest thousandth of a second both in Lead V_1 and in leads from the cavity of the right ventricle. In some instances these measurements were extended to other leads or other deflections.

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*All measurements were made by means of a device designed by Captain B. H. Eliot and manufactured by The Cambridge Company, Ossining, N. Y.

OBSERVATIONS

Extrasystoles.—Premature ectopic beats occurred frequently in some patients and infrequently or not at all in others. Auricular extrasystoles appeared while the catheter was in the right auricle in only one case (Fig. 2). Ventricular extrasystoles, however, were recorded on several occasions when the catheter was in Position II or III in the right ventricle, and could be made to disappear by withdrawing the catheter a few centimeters.

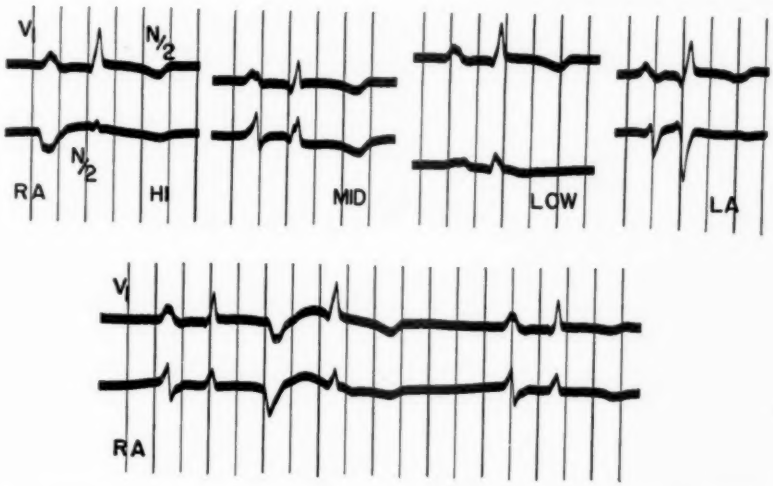

Fig. 2.—Tetralogy of Fallot. Upper beam, Lead V_1 taken with the electrocardiograph at one-half the normal (*N/2*) sensitivity. Lower beam, tracings from high (*Hi*), mid-, and low positions in the right auricle, and from the left auricle (*LA*). The lower strip is a lead from the mid-position in the right auricle and the second complex represents an auricular extrasystole followed by a compensatory pause.

In the type of ventricular extrasystoles usually seen, Lead V_1 displayed a broad, bizarre QS complex (or a broad S wave preceded by a tiny R wave), and in the leads from within the right ventricle the normal initial positivity disappeared, so that the QRS complex was represented by a broad, downward deflection (Fig. 7). Such extrasystoles were attributed to a focus on the endocardial surface of the right ventricle. In one tracing, however, an ectopic ventricular beat occurring after a period of cardiac standstill induced by carotid sinus pressure is represented in Lead V_1 by a deep, broad S wave, preceded by a very small R wave, and in a lead from the cavity of the right ventricle (Position II), by a QRS complex consisting of a broad, notched R wave followed by a small S wave (Fig. 3). It is not certain that this ectopic beat was initiated by the presence of the catheter, but if it arose on the endocardial surface of the right ventricle, the electrocardiographic pattern which it produced is difficult to explain. In that case one would anticipate initial negativity of the ventricular cavity. It clearly had its origin near the cardiac base, for during the larger part of the QRS interval the excitation was spreading away from the precordial electrode near the base and toward the cavity electrode which was near the apex. There is a widespread belief that extrasystoles usually originate in the Purkinje system.[7]

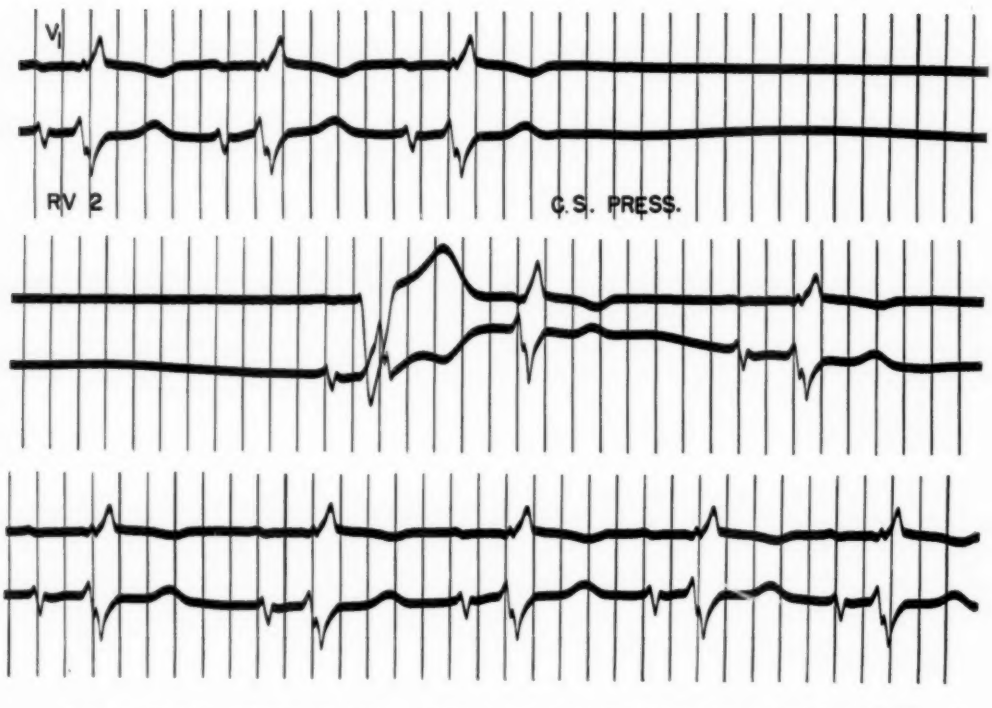

Fig. 3.—Right bundle branch block. Upper beam, Lead V_1. Lower beam, lead from Position II in cavity of right ventricle taken at N/3 sensitivity. The three strips are continuous. Upper strip shows the beginning of prolonged pause following carotid sinus pressure. First complex in the second strip represents an ectopic beat (see text).

Endocardial Effects.—Upward displacement of the RS-T and P-R segments of variable magnitude occurred when the catheter came in contact with the endocardium of the right ventricle or right auricle (Fig. 5). The muscle region affected was obviously small, for displacement of the RS-T segment was never detected in the lead from the right side of the precordium (V_1). When the catheter was withdrawn one or two centimeters, the displacement in the cavity lead promptly disappeared and the first part of the QRS complex recorded from the new position generally resembled in form that recorded when the catheter was in contact with, or very close to the endocardium. In a few instances, however, it was noted that the peak of the initial R wave in the earlier tracing was considerably later (Fig. 8) than in that recorded after the catheter tip had been pulled back. This would seem to indicate that pressure of the catheter against the endocardium may in some instances delay conduction in the right Purkinje plexus, in one of the subdivisions of the right bundle branch, or in this structure itself. In one case of hypertension complete right bundle branch block was present only during the catheterization procedure.

Artifacts.—Occasionally, small, broad, positive waves (Fig. 4) occurred at regular intervals without relation to the heart beat. In a few instances these occurred sporadically. No explanation for these rhythmic deflections can be offered.

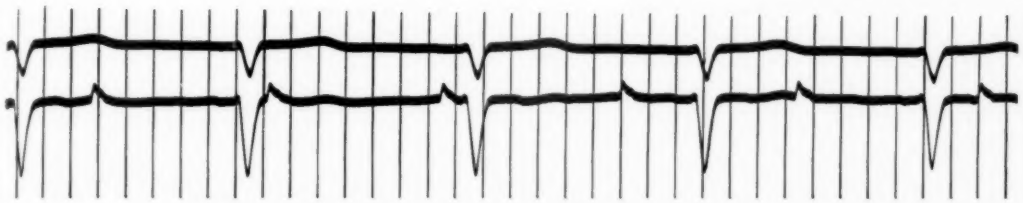

Fig. 4.—Case of hypertension. Rhythmic artifacts of unknown origin. Upper beam, Lead V_1 normal sensitivity. Lower beam, lead from Position II displaying broad, positive waves occurring fairly regularly but bearing no relation to the events of the cardiac cycle. P waves can be seen indistinctly in both upper and lower tracings and the P-R interval is constant.

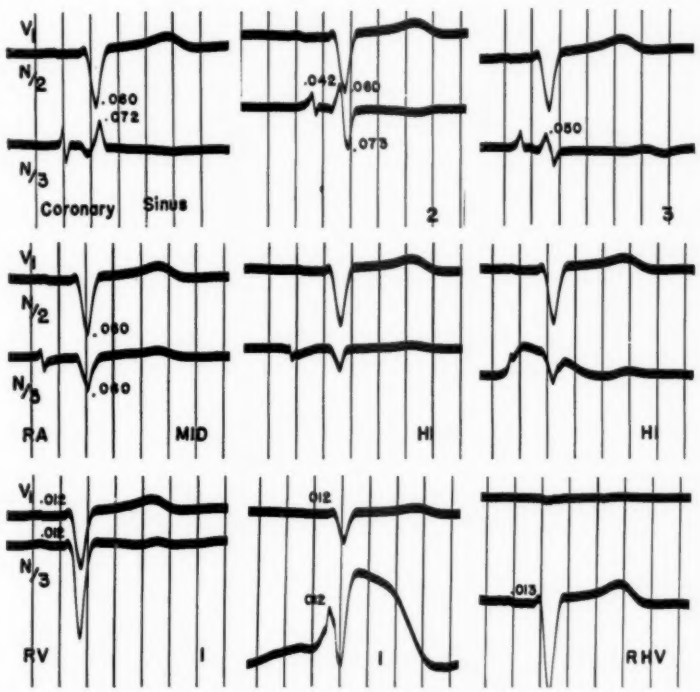

Fig. 5.—Essential hypertension. Upper beam, Lead V_1 taken at N/2 sensitivity. In the second strip of the third row the sensitivity of the upper beam is less than normal and in the third strip it has diminished to almost zero. The lower beam of the upper row shows leads from three different positions in the coronary sinus and in contrast to the leads from the auricular cavity exhibits a short P-R interval and larger R deflections. Lower beam of the second row, leads from the right auricle. The third strip in this row is from the same region as the second, but the electrode was against the auricular wall. In the third row the lower beam represents a lead from Position I in the right ventricle; first, with the catheter free in the cavity, and second, with the catheter in contact with the endocardium. The third and last strip is a lead from the right hepatic vein; the ventricular complex is like that of the intracavitary leads except that the T wave is upright.

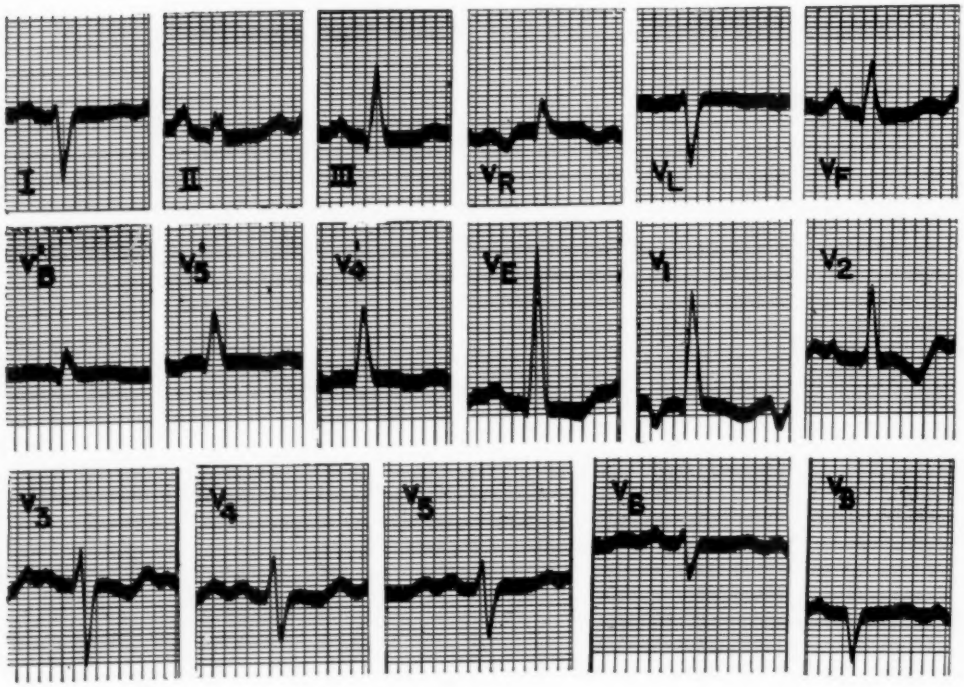

Fig. 6*A*. Tetralogy of Fallot. Standard and augmented unipolar limb leads. Second and third rows show six standard precordial leads; a lead from the ensiform process (V_E); a lead from the angle of the scapula at the level of the apex (V_B). The V'_3 is a lead from a point on the right side of the chest corresponding to the point on the left side from which V_3 is taken. The symbols V'_4, V'_5, etc., have the same significance.

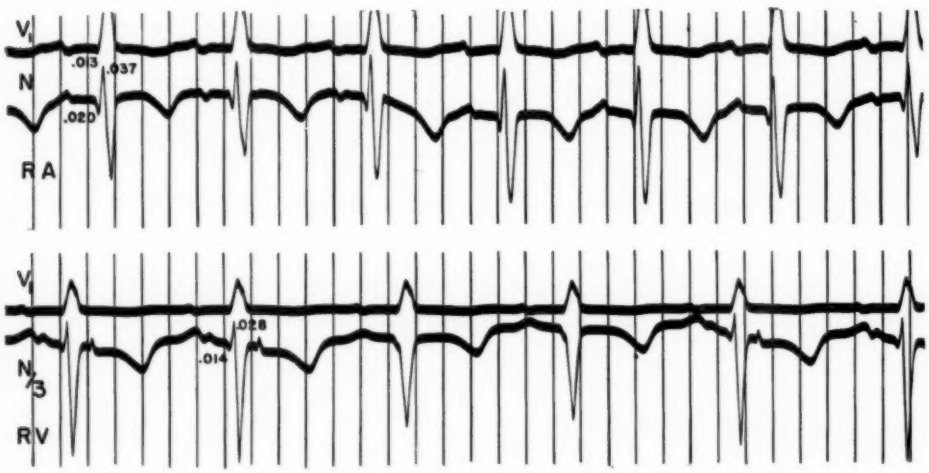

Fig. 6*B*.—Same patient as Fig. 6*A*.—Upper beam, Lead V_1. In the upper row Lead V_1 is at normal sensitivity and the lower beam shows a lead from the right auricle taken at normal sensitivity. The variations in the form of the complexes are due to respiratory changes in the position of the electrode (see text). In the lower strip V_1 is at N/2 sensitivity and the lower beam shows a lead from within the right ventricle taken at N/3 sensitivity. Here also the variations in the form of the complexes are due to respiratory movements of the catheter tip.

Intra-auricular Electrocardiograms.—In general, our observations are in agreement with those of previous workers[4,5,6] and are in accord with the predictions of the dipole theory.[8] When the catheter tip is above the sinus node so that the auricular excitation wave spreads away from it, the P wave lies entirely below the isoelectric level. When the exploring electrode is in the middle of the auricular cavity so that the impulse first approaches, and then passes it, the P wave is of the RS type, with the peak of the R wave representing the arrival of the impulse at the level of the electrode. In leads from the lowest portion of the auricular cavity the P wave is predominantly positive (Fig. 7). In one instance it was observed that the auricular complex regularly passed through the three forms, that is, from positive to diphasic to negative, while the P-R interval remained constant (Fig. 6*B*). It was apparent that this cycle was due to respiratory variations in the position of the catheter tip. In a few instances we were able to produce similar changes in the P waves by instructing the pa-

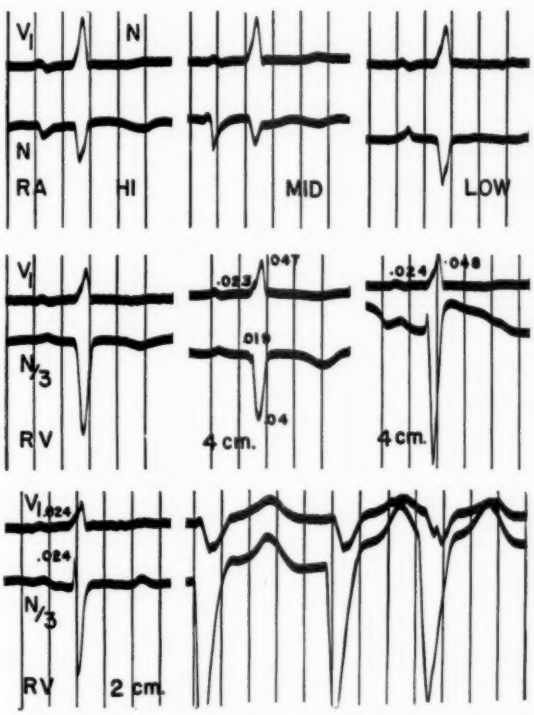

Fig. 7.—Tetralogy of Fallot. Upper beam, Lead V_1. The electrocardiograph was adjusted to normal sensitivity, but because of the condition of the batteries the sensitivity gradually fell to approximately N/2. Lower beam, upper row; leads from the right auricle. First strip of second row shows a lead from Position I in the right ventricle. The next two strips show leads from the right ventricle; fluroscopic control showed the catheter tip to be 4.0 cm. to the left of the midsternal line. The catheter was against the endocardial wall when the second strip was taken. Lower beam, third row, shows a lead from within the right ventricle with the catheter tip 2.0 cm. to the left of the midsternal line. The last three complexes represent extrasystoles with the catheter at the same position. Note the close correspondence between the R wave of the cavity lead and the notch in V_1 when the catheter was not against the wall. The small numbers to the third decimal place indicate the time in seconds of the adjacent peak with reference to the beginning of the QRS interval.

tients to breathe deeply. With the electrode in the midauricular position, the P waves were of the RS type during quiet respiration. During inspiration the electrode shifted to the upper portion of the auricle, and the P wave was of the QS type, whereas in expiration when the electrode moved into the lower portion of the auricular cavity, the P wave was upright.

In one case of congenital heart disease the P waves in the leads from the right side of the precordium were broad and notched. Because of the presence of a patent interauricular septal defect, it was possible in this instance to obtain electrocardiograms from the midportions of both the right and left auricles. In the lead from the right auricle the intrinsic deflection corresponded in time to the first notch of the P wave of Lead V_1. In the lead from the left auricle the P-R interval was shorter and the intrinsic deflection corresponded in time to the second notch of the P wave in the precordial lead. The QRS complex of the lead from the right auricle differed strikingly from that of the lead from the left. The former was dominated by a large R wave, whereas the chief deflection of the latter was downward (Fig. 2). The patient had extreme right ventricle enlargement and it is suggested that the lead from the right auricle reflected the late activation of the base of the hypertrophied right ventricle, and that from the left auricle, the negativity of the left ventricular cavity.

In another instance, fluoroscopy, blood sample showing an oxygen content of seven volumes per cent, and extremely low pressure readings indicated that the catheter was in the coronary sinus. The tracing from this region, that is, the groove between the left auricle and the left ventricle, displayed a shorter P-R interval than that from the right auricle. This observation may be regarded as additional evidence that the left auricle is activated later than the right. The patient had left ventricular enlargement. In contrast to the observations on the patient with right ventricular enlargement, previously described, the QRS complex of the lead from the right auricle consisted of a QS wave. In the leads from different positions in the coronary sinus, however, the QRS complex displayed a prominent R wave (Fig. 5). These positive waves differed in time from one position to another and it is suggested that they reflect the activation of different portions of the base of the left ventricle.

Previous workers[4,5] have noted that the complexes of leads from the upper levels of the right auricle are often similar in form to those of Lead V_R. The majority of our cases showed a resemblance of this kind. There were a few instances, however, in which the form of the QRS complex in Lead V_R was like that of the leads from the lower portion of the right auricle. Sometimes the QRS complex of the leads from the auricle displayed a prominent Q wave which preceded in time the initial positive ventricular deflection of the leads from the right ventricle. We have no adequate explanation for this early auricular negativity, but it is necessary to consider that an electrode in the right auricle may reflect the potential variations produced by the left, as well as those produced by the right ventricle.

Intraventricular Electrocardiograms.—Other investigators[4,5,6] have observed that as a rule the cavity of the right ventricle is positive at the beginning of the

QRS interval. This initial positivity has been attributed to early activation of the upper portion of the septum from left to right; in other words, to what may be considered physiologic incomplete right bundle branch block. An initial R wave was present in the leads from the cavity of the right ventricle in all of our cases. The amplitude of this early R wave varied, however, with the position of the catheter within the right ventricle. The R wave of the lead from Position I was frequently smaller than that of the leads from Positions II and III; and, in a few instances it was absent so that the QRS complex was represented by a QS deflection (Fig. 7). This deflection often displayed a notch or slur on the descending limb, corresponding in time to the R wave recorded in the lead from Position II or III in the same case. When these notches or slurs occurred, they were not constantly present, but came and went rhythmically. In one instance, with the catheter tip at Position I there were periodic transitions from an uncomplicated QS wave, to one notched on its descending limb, and from this form to a complex of the RS type. In this case (Fig. 6*B*) there was an intraventricular septal defect, and we considered the possibility that the catheter tip was entering and leaving the left ventricle. It may well be, however, that the variations in question were due to changes in the position of the exploring electrode in relation to the septum. As in the case of the similar variations in the auricular complex seen in auricular leads, we examined the effect of respiration upon the form of the complexes of intraventricular leads in several instances. It was found that during deep inspiration, which would be expected to shift the tip of the catheter toward the base of the heart, the initial R wave sometimes became smaller, whereas expiration made it larger (Fig. 9*B*). This finding is in accord with the observation that the R wave is ordinarily smaller in the lead from Position I than in that from Position II or III. It seems to us necessary to reexamine the concept that the uppermost part of the left side of the septum is activated earlier than any other.

The P waves of the intraventricular tracings were generally small and upright and the T waves were usually inverted. Exceptions to the latter rule will be discussed in a later section.

Relations Between Precordial Lead V_1 and Leads From the Right Ventricle.— Since V_1 is the precordial lead which is thought to reflect best the potential variations of the surface of the right ventricle, it was considered desirable to compare this lead with the leads from different points within the right ventricle. We hoped in this way to obtain a better understanding of the form of the ventricular complex in leads from the right side of the precordium, particularly in cases of right ventricular enlargement and right bundle branch block. Before presenting the findings in each of our four groups of patients, it seems appropriate to consider briefly a few of the concepts involved in a discussion of this type.

Let us consider, to begin with, the forces produced by activation of the septum in a direction perpendicular or nearly perpendicular to its endocardial faces. The potentials of the two ventricular cavities may be expected to differ in sign only when there are one or more boundaries between active and resting muscle in the septum. When one side of the septum is activated before the other, the

homolateral cavity is initially negative and the contralateral, initially positive. The normal, initial positivity of the right ventricular cavity in man is, therefore, attributed to early activation of the septum from left to right.

We may conclude, then, that activation of the septum in the normal fashion has opposite effects upon the potentials of the two cavities. It has the same effect upon each cavity and the epicardial surface of the free ventricular wall which bounds it. In contrast, the activation in the normal fashion of one of the free ventricular walls has opposite effects upon the potentials of its inner and outer surfaces, but affects the potentials of both ventricular cavities in the same way. These statements, of course, concern the sign of the potentials referred to, not their magnitude. When a boundary between active and resting muscle is established between the cavity and the epicardial surface of the right ventricle by an impulse spreading through its free anterior wall from within outward, the presence of this boundary will tend to make the epicardial surface of the wall positive and the ventricular cavity negative. The potential of the precordium is under all ordinary circumstances of the same sign with reference to an indifferent point, such as the central terminal, as that of the nearest part of the epicardial surface. But the magnitude of the potential of the precordium in comparison with that of the nearest part of the epicardium is dependent upon a variety of factors and is not easily predictable.

With reference to the comparison of the ventricular complexes of a lead from the right side of the precordium and the ventricular complexes of a lead from the cavity of the right ventricle, the following conclusions seem to be justifiable when, but only when, the ventricles are responding to impulses which reach them solely by way of the bundle of His, regardless of whether all subdivisions of this bundle are conducting normally. When a deflection in one direction occurs in the precordial lead simultaneously with a deflection in the opposite direction in the cavity lead, both deflections should be attributed to forces across a boundary between active and resting muscle in the free wall of the right ventricle. On the other hand, when a deflection in one direction in the precordial lead occurs simultaneously with a deflection in the same direction in the cavity lead, it is justifiable to conclude that the cavity deflection is shaped by forces arising at a boundary between active and resting muscle lying in the ventricular septum or the free wall of the left ventricle. The precordial deflection must be attributed in part to the same forces, but the possibility that it also represents forces generated in the free wall of the right ventricle cannot be excluded.

The initial activation of the septum from left to right which normally occurs prior to the activation of the free wall of the ventricles is represented by an R wave in the leads from the precordium which reflect the potential variations of the right side of the septum (Lead V_1, and possibly Leads V_2 and V_E) and by a Q wave in those leads which reflect the potential variations of the left side of the septum (Leads V_5 and V_6 in about 50 per cent of normal subjects and leads from the left back).

In normal subjects and in patients with left ventricular enlargement, the small initial R deflection which occurs in the leads from the right side of the

precordium is more or less simultaneous with the initial R wave of the leads from the cavity of the right ventricle. It is justifiable, therefore, to conclude that the precordial R wave is due in part to forces of septal origin. After the inscription of this initial R wave the precordium and the cavity of the right ventricle are negative, and it is clear that this negativity is due to activation of the septum from right to left, to activation of the free walls of the two ventricles from within outward, or to both. The rapid increase in the negativity of the right ventricular cavity early in the QRS interval, for which these septal and left ventricular forces are responsible, causes the part of the precordial R wave due to activation of the thin free wall of the right ventricle to be much less conspicuous than it would be if it were written on a horizontal base line instead of a steep downward slope. The size of this R wave is not proportional to the voltage across the right ventricular wall. In right ventricular hypertrophy, on the other hand, the activation of the thick free wall of the right ventricle produces voltages that are greater or develop more rapidly than the septal and left ventricular forces in question and are also of longer duration. Under these circumstances the potential of the epicardium of the right ventricle and the right precordium are positive for a considerable period during which the potential of the ventricular cavity is negative. In right bundle branch block the activation of the free wall of the right ventricle occurs so late in the QRS interval that the forces which it produces are unopposed. Here again the potential of the cavity and the potential of the epicardial surface of the right ventricle are opposite in sign.

The principles applicable to interpretation of the deflections produced by depolarization are equally valid in the interpretation of those which accompany repolarization. The T wave in leads from the epicardial side of the free wall of the right ventricle will differ in direction from that inscribed in leads from the ventricular cavity side only when the forces produced by repolarization of the free wall of the right ventricle are not overbalanced by those produced by repolarization of other parts of the heart. In the majority of normal adults the T waves are upright in the leads from the right side of the precordium and inverted in leads from the right ventricular cavity. This implies that repolarization takes place earlier on the epicardial than on the endocardial side of the right ventricular wall; in other words, the repolarization process spreads from the epicardial toward the endocardial surface. When the T waves have the same direction in leads from both sides of the free wall of the right ventricle, their form is evidently determined to a large extent by forces produced by repolarization of the septum or the free wall of the left ventricle. Under these circumstances the present method of investigation does not furnish reliable information concerning the direction of repolarization in the free wall of the right ventricle. Such information could be obtained only by measuring the voltage across the wall during the inscription of the T wave by leading from its endocardial to its epicardial surface.

Group. 1. Cases of Right Ventricular Enlargement.—The majority of our cases of this kind were examples of extreme right ventricular enlargement. The precordial electrocardiogram, therefore, was of the type displaying tall R

waves in the leads from the right side of the precordium and small R and deep S waves in the leads from the left side (Fig. 6*A*). In one case in which the clinical diagnosis was tetralogy of Fallot the large R deflection of the leads from the right side of the precordium was preceded by a Q wave (Fig. 6*A*). The leads from within the right ventricle also displayed a Q deflection and this was simultaneous with the Q wave in lead V_1 (Fig. 6*B*). It can hardly be doubted that the precordial Q wave and the cavity Q wave are alike in origin, but there is no entirely satisfactory explanation for the occurrence of a Q deflection in leads from the right ventricular cavity. Several possibilities may be considered. There was no Q wave in the leads from the left side of the precordium and the left side of the back, but this deflection occurred in all the leads from the right side of the precordium and in a lead from the posterior aspect of the right chest (Fig. 6,*A*). If the R wave of the cavity lead in this case is attributed to activation of the left side of the septum before the excitation process reached the right side by way of the right branch of the bundle of His, the still earlier Q deflection must be ascribed to an excitatory process traveling away from the exploring electrode through left ventricular muscle. If the cavity Q wave were due to forces arising in the free wall of the right ventricle, it would be expected to be simultaneous with an upward deflection in Lead V_1. If we ascribe this deflection to activation of the septum from right to left, we must assume that the right side of the septum was activated before the left; or, that the two sides of the septum were activated simultaneously and the forces produced by activation of the right side of this structure overbalanced those produced by activation of its left side during the earliest phases of the QRS interval. It seems unlikely that there is a minor defect in left bundle branch conduction in those cases of right ventricular hypertrophy in which the right ventricular cavity is initially negative, for this hypothesis does not satisfactorily account for the rather prominent R wave which follows the small Q wave in right cavity leads. It is conceivable that in these cases excitation begins or develops most rapidly in the free wall of the left ventricle or in one of the papillary muscles in the left or right side of the septum. Whether the presence of a defect in the ventricular septum is in any way responsible for the phenomenon in question is also a matter for conjecture. It is hardly worth while to speculate further until more data are available, but it should be noted that occasionally in dogs there is initial negativity of the right ventricular cavity, even in the presence of right bundle branch block.[2, Fig. 6]

Four of our patients with right ventricular enlargement displayed notching or slurring of the upstroke of the tall R wave of Lead V_1. In three of these the R-wave peak in the cavity lead corresponded closely in time to the notch or slur in Lead V_1 and the peak of the R wave in the precordial lead was related closely in time to the S deflection of the leads from the cavity of the right ventricle (Fig. 7). It seems evident, therefore, that in cases of this type the R wave in Lead V_1 represents forces produced by activation of the septum from left to right followed closely by the activation of the free wall of the right ventricle from within outward. The form of the precordial QRS complex in these cases is reminiscent of that seen in cases of complete right bundle branch block. In these the QRS interval is longer (0.12 second or more), but the R wave of

Lead V_1 is often conspicuously slurred and notched. Leads from points farther to the right, however, usually display double R waves. In the cases with which we are dealing, the QRS interval measured less than 0.10 second, but because of the form of the QRS complex in Lead V_1, incomplete right bundle branch block was frequently suspected. The initial R deflection in the leads from the right ventricular cavity in our four cases, however, does not differ appreciably from that recorded in normal subjects. Furthermore, leads from points to the right of the right sternal margin did not display double R waves. Thus, it seems unlikely that more than the physiologic degree of incomplete right bundle branch block was present in these cases.

In five of the six cases of Group 1, Lead V_R displayed a late R wave and the QRS complex of this lead resembled that of one or more of the leads from the cavity of the right auricle.

In three cases the T waves were upright in the leads from the right side of the precordium and inverted in those from the right ventricular cavity. This pattern is the rule in normal subjects and, as already noted, suggests that repolarization takes place earlier on the epicardial side than on the endocardial side of the right ventricular wall. In the other three cases the T waves were inverted both in the leads from the right side of the precordium and in those from the right ventricle, and this T-wave pattern is ascribed to the course of repolarization in parts of the heart other than the free wall of the right ventricle. It does not permit any conclusion as to whether repolarization of this wall begins on its inner or outer surface. It should be noted, however, that in all six cases of right ventricular enlargement the QRST area of the cavity leads was clearly negative, whereas that of Lead V_1 was clearly positive. This indicates that the gradient in the length of systole, or speaking more strictly, in the time course of excitation and recovery, across the free wall of the right ventricle was of the same kind in all of them.

Group 2. Right Bundle Branch Block.—The two patients in this group had moderate hypertension. One patient displayed complete right bundle branch block only during catheterization, and it is possible that the conduction defect was initiated by this procedure. The other patient was unusual in that the right bundle branch block usually disappeared when the heart rate was reduced by carotid sinus pressure. During the catheterization carotid sinus pressure caused pronounced cardiac slowing but did not abolish the block (Fig. 3).

In both cases there was a broad, initial R wave in the leads from the right ventricle. As in the other cases the size of this deflection varied with the level of the electrode, and in both instances its voltage was smaller in the lead from Position I than in the lead from Position II. In each case it was clear that the initial positivity of the cavity was responsible, at least in part, for the early R wave in Lead V_1, whereas the S wave of the intraventricular lead corresponded in time to the late R′ of the precordial tracing. In one case the precordial R wave was distinctly bifid and the late R′ had a notch on its descending limb (Fig. 8). This notch corresponded in time to the nadir of the S wave of the intraventricular lead, and this part of R′ is clearly attributable to the activation of the

free wall of the right ventricle. The depression which separates the R and R′ deflections in Lead V_1 corresponds in time to the notch on the intraventricular R wave and it seems likely that both represent the effect of forces produced by activation of the free wall of the left ventricle. Thus, in those cases of complete right bundle branch block in which the secondary R′ wave in Lead V_1 is broad, and particularly when it is notched, the first part of this deflection is evidently due mainly to activation of the septum from left to right, whereas its final part represents activation of the free wall of the right ventricle. In cases of right bundle branch block in which the R′ deflection of Lead V_1 is slender and unnotched, it is still uncertain whether it is due solely to activation of the free wall of the right ventricle, or contains septal components also.

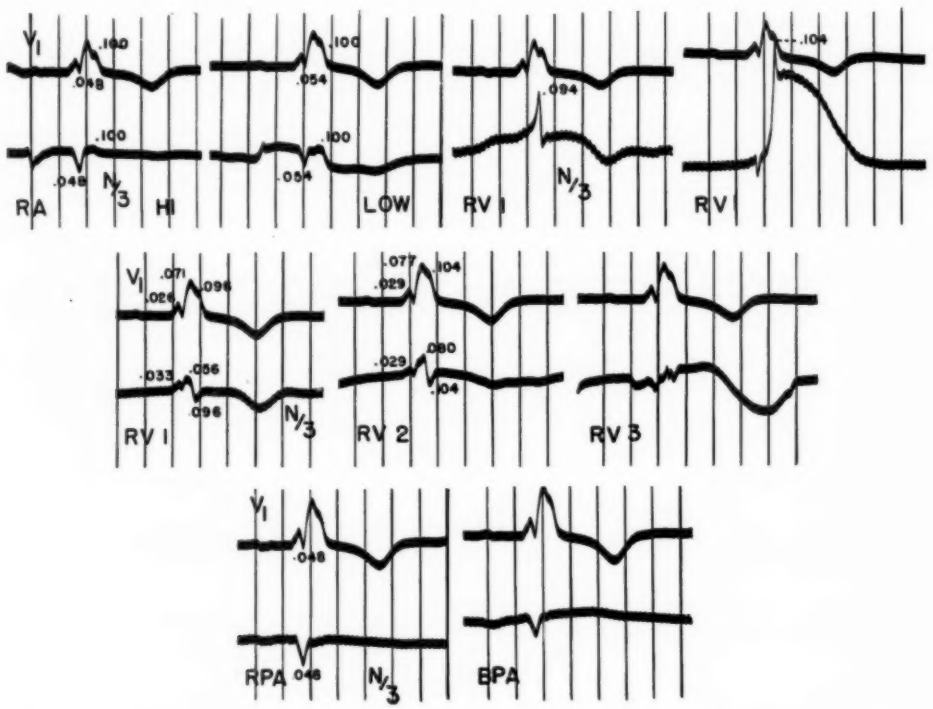

Fig. 8.—Right bundle branch block. Upper beam, Lead V_1. Upper row, the first two strips show leads from the right auricle. The last two strips show a lead from Position I in the right ventricle, with the catheter tip first about 1.0 cm. from the endocardium and then in contact with it. The second row shows leads from three positions in the right ventricle. The tracing from Position III shows numerous artifacts. The two strips of the third row show leads from the right pulmonary artery (*RPA*) and the bifurcation of the pulmonary artery (*BPA*). The small numbers record in seconds the time of the adjacent peaks in relation to the beginning of the QRS complex in Lead V_1 or in the cavity lead.

One of our records shows a QRS complex of the normal type, indicating that the bundle branch block temporarily disappeared. In Lead V_1 this complex is of RS form and measures 0.08 second in duration. In the lead from the right ventricle the same beat is represented by a QS complex or a downward deflection preceded by a tiny R wave. The intracavitary R wave measured 0.04

second in duration in one and 0.09 second in the other case of right bundle branch block. In our other cases the duration of this deflection averaged about 0.02 second, the minimum being 0.010 second and the maximum, 0.035 second (the latter occurring in the tracing of a normal subject). The height of this R wave deflection in the two cases of right bundle branch block was no greater than its height in our other cases, and it seems unlikely that its voltage can be depended upon to differentiate between right bundle branch block and normal intraventricular conduction. On the other hand, its duration may be helpful in making this differentiation.

In our two cases of right bundle branch block the intra-auricular leads displayed a broad, late R wave similar to that present in Lead V_R.

Group 3. Left Ventricular Enlargement.—There were three patients in this group, all with prominent left ventricular enlargement. In all of them the leads from the right ventricle displayed a small initial R wave (Figs. 5 and 9*B*). The duration of this deflection was approximately the same as in the cases of right ventricular enlargement, but on the whole its amplitude was smaller. If its small size were due to less early activation of the left side of the septum, one would expect the Q waves of the leads from the left side of the precordium to be correspondingly reduced in size. In the few patients whom we were able to examine, this was not the case. There are cases of left ventricular enlargement in which the initial R wave of the leads from the right side of the precordium is minute or entirely absent and intracavitary leads would be of great interest in such cases. No cases of this kind are included in our series.

In two cases there was a late R wave in the leads from the lower portion of the right auricle (Fig. 9*B*). It is suggested that this deflection was due to activation of the base of the left ventricle. In one of these Lead V_R displayed a similar deflection (Fig. 9*A*). In the remaining two cases the QRS complex of Lead V_R consisted of a QS complex.

The T waves were inverted in the intraventricular leads in one case and low but upright in the other two. The T waves were upright in the leads from the right side of the precordium but inverted in all those from the left side in all three cases.

Group 4.—The remaining four patients form a heterogeneous group, but in none was cardiac enlargement present. The intracavitary R waves corresponded closely in time with the R waves of Lead V_1. In all instances but one the initial R wave of the right ventricular cavity measured less than 0.024 second in duration and was not conspicuously tall. The exceptional patient was a young man of twenty without apparent heart disease whose tracings in the leads from the right ventricle displayed R waves which were unusually broad (0.035 second) and tall compared with the S wave (Fig. 10*B*). This patient's precordial electrocardiogram showed a QRS interval of 0.09 second, tall R waves in the leads from the right side of the precordium, especially Lead V_E, and Q waves in Leads V_5 and V_6 (Fig. 10*A*). In Lead V'_4 (a lead from the right side of the chest corresponding to Lead V_4) the sole QRS deflection was upward. We have

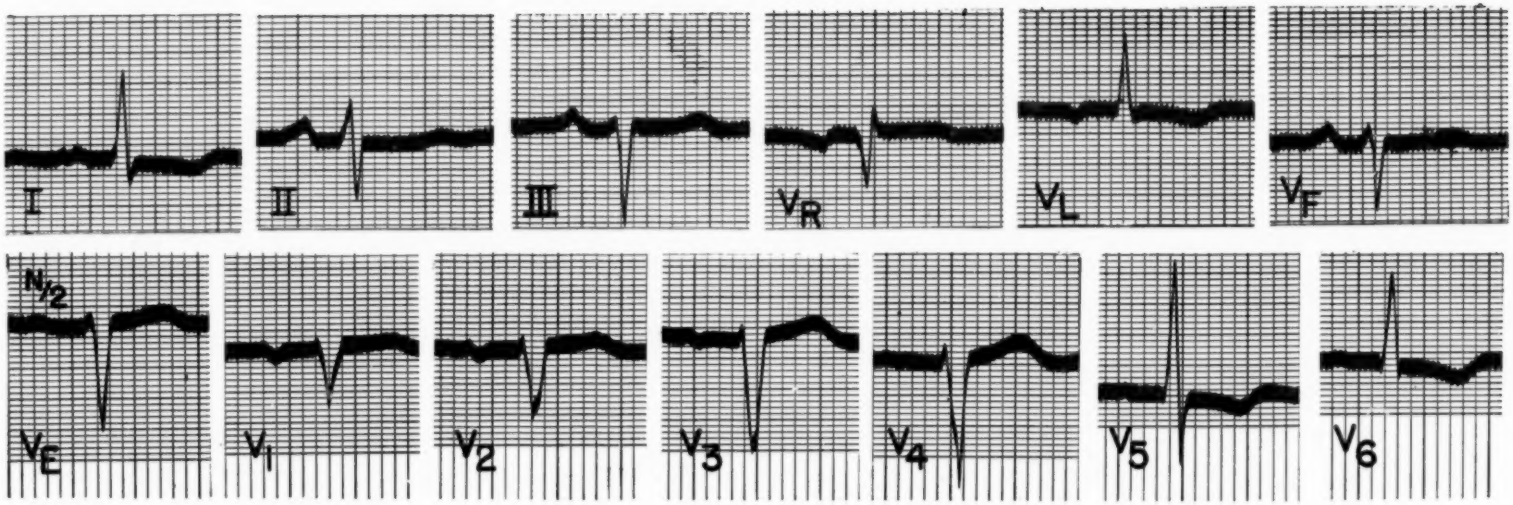

Fig. 9A.—Essential hypertension. Upper row, the standard and augmented unipolar leads. Lower row, precordial electrocardiograms recorded at N/2 sensitivity.

wondered whether an abnormal delay in the activation of the right ventricle was present in this case. Certainly, if intracavitary leads and leads from the right side of the chest had not been taken, no abnormality would have been suspected. It is our opinion that in some normal subjects the normal difference in the time of activation of the two ventricles is greater than it is in others.

SUMMARY AND CONCLUSIONS

Intracavitary electrocardiography is useful for the purpose of ascertaining the effects of activation of the free wall of the right ventricle upon the form of the QRS complex of Lead V_1 in cases of right ventricular enlargement and right bundle branch block. The order in which the inner and outer layers of this wall are repolarized is disclosed by this method only when the T waves of the leads from the ventricular cavity and those of the leads from the right side of the precordium are opposite in direction.

1. In right ventricular enlargement the large R wave in Lead V_1 represents the activation of the free wall of the right ventricle. Notches or slurs on the upstroke of this deflection are apparently due to the activation of the septum

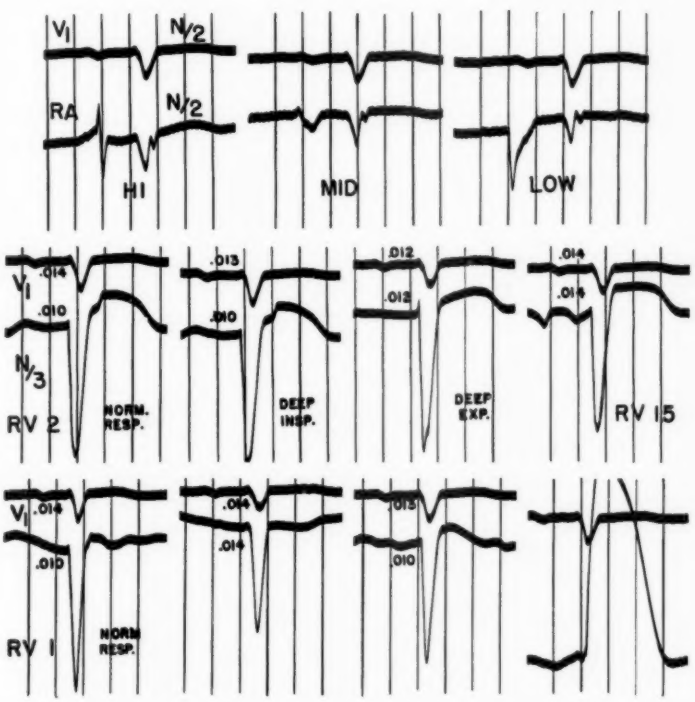

Fig. 9*B*.—Same patient as Fig. 9*A*. Upper beam, Lead V_1. First row, leads from the right auricle. Second row, the first three tracings show a lead from Position II in the right ventricle during normal respiration, deep inspiration, and expiration, respectively. Last tracing of the second row is from position in the right ventricle midway between Positions I and II. Lower row, leads from Position I in the right ventricle during normal respiration, deep inspiration, and expiration, respectively. Last tracing taken when catheter tip was against endocardium at Position I.

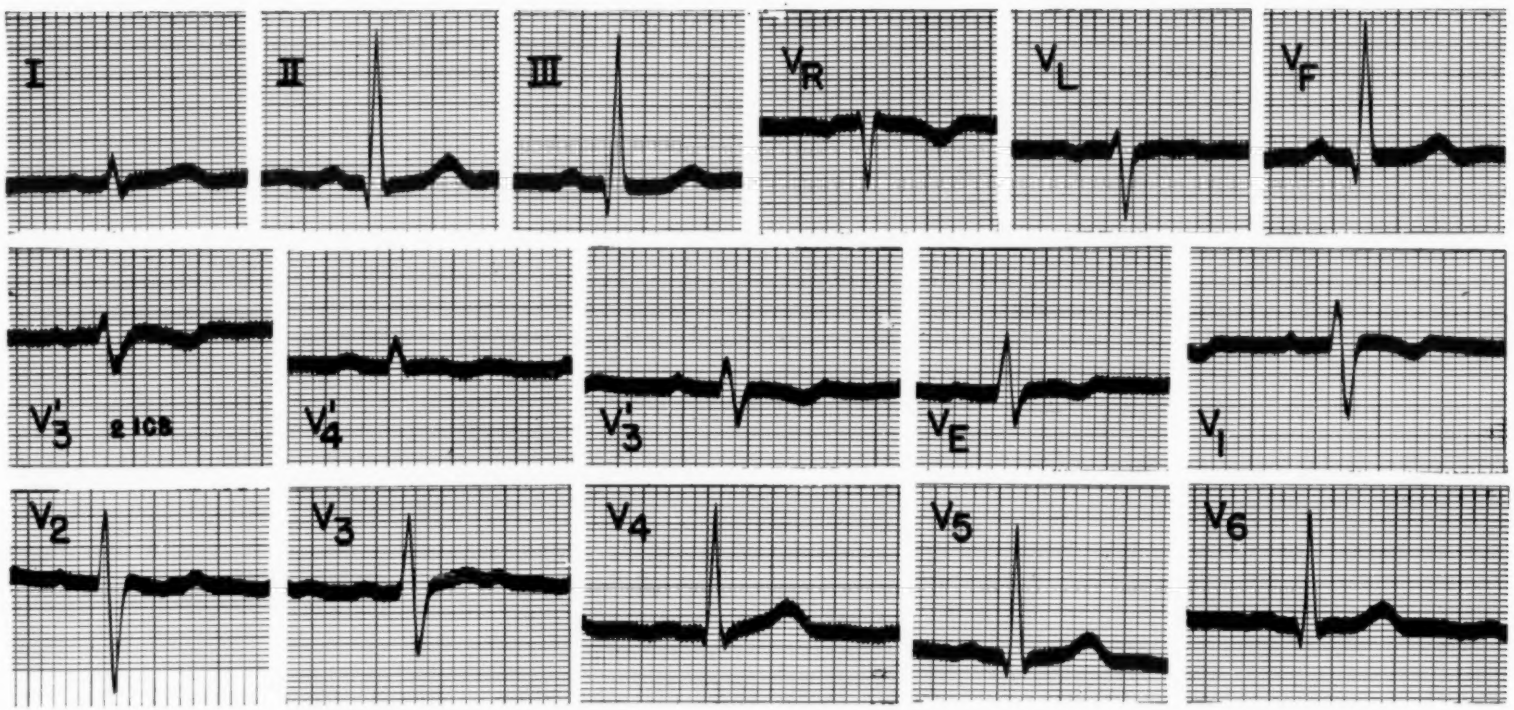

Fig. 10*A*.—Normal subject. Upper row, standard and augmented unipolar limb leads. Lower rows, leads from the chest. Symbols have the same significance as in previous figures. Lead V'_3 was taken at the usual position and also at the second intercostal space.

from left to right and do not justify the conclusion that the right ventricle is activated abnormally late. In some cases of right ventricular enlargement in which there is a Q deflection in Lead V_1, there is a simultaneous Q deflection in leads from the cavity of the right ventricle. The origin of this Q wave is obscure.

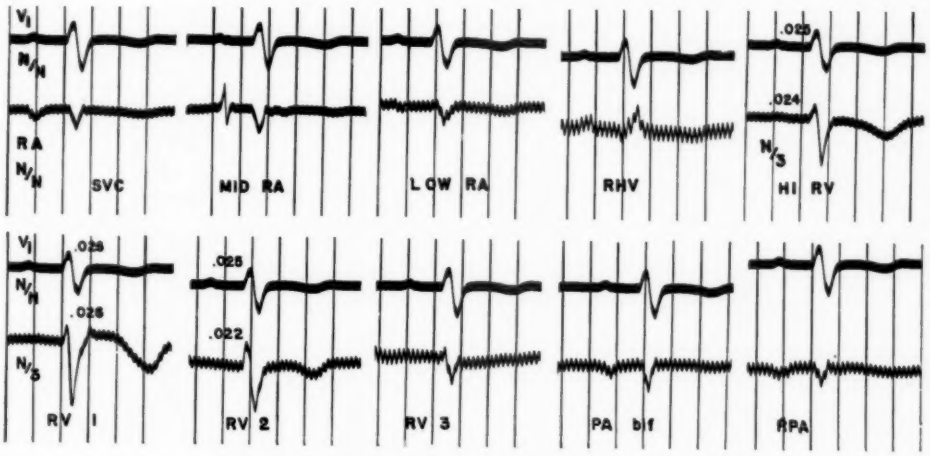

Fig. 10*B*.—From the same patient as Fig. 10*A*. Upper beam, Lead V_1. Lower beam, leads from superior vena cava (*SVC*), mid-position in the right auricle (*mid RA*), lower position in the right auricle (*low RA*), and right hepatic vein (*RHV*). *Hi RV* is the same as Position I in the right ventricle (RV_1), but the latter is from a point closer to the endocardium. RV_2 and RV_3 equal Positions II and III in the right ventricle. Last two strips show leads from the bifurcation of the pulmonary artery (*PA bif*) and from the right main branch of the pulmonary artery. Unfortunately, 60 cycle current was superimposed on several of the tracings.

2. In right bundle branch block the initial R wave in Lead V_1 is due to the activation of the septum from left to right. In those electrocardiograms in which the secondary R wave in Lead V_1 is broad and notched, the initial portion of this secondary R wave is due to the activation of the septum, and its final portion, to activation of the free wall of the right ventricle.

The height of the intracavitary R wave is not a useful criterion for the purpose of diagnosing conduction defects in the right branch of the bundle of His, but its duration may prove to be of greater value.

3. In normal subjects and in patients with left ventricular enlargement, the early activation of the septum from left to right contributes to the R wave of Lead V_1 and is responsible for the Q wave that occurs in Leads V_5 and V_6.

4. Leads from the cavity of the right auricle and Lead V_R usually reflect the late activation of the base of the right ventricle when it is hypertrophied, and may in other instances reflect the late activation of the base of an hypertrophied left ventricle.

5. In some normal individuals the difference in the time of activation of the two ventricles is greater than in others. This greatly complicates the diagnosis of incomplete right bundle branch block.

6. In the free wall of the right ventricle the repolarization process ordinarily advances from the epicardial toward the endocardial surface.

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DURATION OF THE Q-T INTERVAL IN NORMAL PREGNANT WOMEN

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MEASUREMENT of the Q-T interval in the electrocardiogram has long been regarded as almost useless for any clinical purpose. It is known to be shortened by digitalis[1] and salicylates[2] and lengthened by hypocalcemia, quinidine, acute myocardial infarction, and congestive heart failure.[3,4] However, since Taran and Szilagyi[5] showed that the Q-T interval is abnormally prolonged in all cases of rheumatic carditis which they observed and that it is not prolonged in inactive rheumatic disease or in normal subjects, it has become a measurement of considerable significance in the evaluation of rheumatic carditis.

Various studies have been made to determine the normal limits of the Q-T interval in normal healthy individuals. These studies have been used as a base line to determine abnormal prolongation. Inasmuch as it is very important to make an early and correct diagnosis of active rheumatic carditis in pregnant women and in order to use the Q-T interval as one of the criteria for activity, it is first necessary to determine the normal range in healthy pregnant women. It seemed possible that the altered circulatory dynamics during pregnancy might have some effect on its duration.

METHOD

Electrocardiograms were taken on fifty normal women from the prenatal clinic. These covered the entire period of gestation. The electrocardiograms, consisting of the three standard limb leads and CF_4, were made with the subjects in the supine position. The instrument used was a Cambridge mobile electric model, with an independent Telechron timer. All measurements were made with the aid of a magnifying lens in all leads in which a clear curve was obtained. The cycle length (R-R) and the Q-T interval were determined from averages of all leads. Taran's modification of Bazett's formula* $\left(\text{Q-Tc} = \frac{\text{Q-T}}{\sqrt{\text{R-R}}}\right)$ was used.[5,6] This modification instead of using a constant K (=0.40) to determine the average normal Q-T at any given rate calculates a corrected Q-T† from any given measured Q-T interval and R-R. This provides an easy method of comparing any determination with a normal standard.

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*$\text{Q-T} = \text{K}\sqrt{\text{R-R}}$.

†Corrected to a cycle length of 1.00 second.

RESULTS

The results of these measurements and calculations are shown in Table I. Q-Tc ranged from 0.371 to 0.421, with an average value of 0.394. These figures are all below the commonly accepted upper limit of normal of 0.425 for adult women. The measured Q-T intervals were plotted against the R-R intervals on a scatter graph (Fig. 1) on which is shown Ashman and Hull's[7] upper limit of normal and average normal, and Bazett's[6] average normal for adult women. It is seen that all the measurements fall below the upper limit of normal and that they follow closely the curves for average normal. Breaking the figures down into the three trimesters of pregnancy gives average Q-Tc values of 0.390, 0.396, and 0.394 for the first, second, and third trimesters, respectively.

TABLE I. DURATION OF PREGNANCY, AGE SPREAD, AND MEASURED AND CORRECTED Q-T INTERVALS IN FIFTY PREGNANT WOMEN

CASE	DURATION OF PREGNANCY (MO.)	AGE (YEARS)	R-R (SEC.)	Q-T (SEC.)	Q-Tc (SEC.)	CASE	DURATION OF PREGNANCY (MO.)	AGE (YEARS)	R-R (SEC.)	Q-T (SEC.)	Q-Tc (SEC.)
1	9	19	0.620	0.325	0.414	26	6	23	0.706	0.329	0.391
2	8½	20	0.740	0.335	0.389	27	4	29	0.619	0.311	0.398
3	8½	20	0.735	0.340	0.397	28	2	23	0.850	0.361	0.392
4	6½	39	0.564	0.291	0.390	29	8	21	0.721	0.323	0.381
5	8	19	0.600	0.298	0.386	30	3	31	0.770	0.333	0.379
6	7½	23	0.762	0.338	0.387	31	3	29	0.763	0.337	0.385
7	2	29	0.660	0.321	0.395	32	5	27	0.705	0.325	0.387
8	6	25	0.658	0.323	0.400	33	3	21	0.680	0.330	0.399
9	9	21	0.655	0.319	0.396	34	9	20	0.635	0.319	0.400
10	3	25	0.480	0.270	0.391	35	5½	31	0.750	0.350	0.405
11	7½	20	0.555	0.315	0.421	36	3	22	0.819	0.360	0.399
12	7	23	0.666	0.311	0.382	37	6½	26	0.570	0.295	0.392
13	4½	25	0.776	0.352	0.399	38	5½	26	0.710	0.349	0.415
14	6	27	0.600	0.320	0.413	39	6	38	0.626	0.331	0.416
15	3½	20	0.704	0.311	0.371	40	9	23	0.854	0.351	0.383
16	4	31	0.749	0.345	0.398	41	5	26	0.521	0.280	0.389
17	8½	32	0.521	0.280	0.389	42	4	21	0.715	0.327	0.387
18	7½	35	0.711	0.339	0.402	43	8	24	0.634	0.302	0.390
19	8½	24	0.570	0.290	0.383	44	8½	23	0.509	0.283	0.397
20	4	25	0.739	0.325	0.379	45	8½	24	0.666	0.318	0.391
21	2½	22	0.760	0.355	0.407	46	7	30	0.615	0.310	0.395
22	6	27	0.650	0.306	0.381	47	8	29	0.635	0.309	0.389
23	3½	24	0.611	0.303	0.389	48	9	20	0.520	0.287	0.397
24	6	24	0.522	0.292	0.403	49	3½	21	0.795	0.340	0.383
25	3	26	0.735	0.320	0.384	50	5	20	0.673	0.320	0.392
						Average			0.656	0.320	0.394

COMMENT

Despite alterations in the circulatory dynamics during pregnancy, there is no significant variation in the duration of electrical systole from the average normal. This knowledge enables one to make use of the Q-T interval in determining the presence and the duration of active rheumatic carditis. Abnormally

prolonged Q-T intervals were found throughout the entire period of activity in three pregnant women admitted to Beth Israel Hospital with acute rheumatic carditis during the past year. Electrocardiograms before and after activity had normal Q-T intervals.

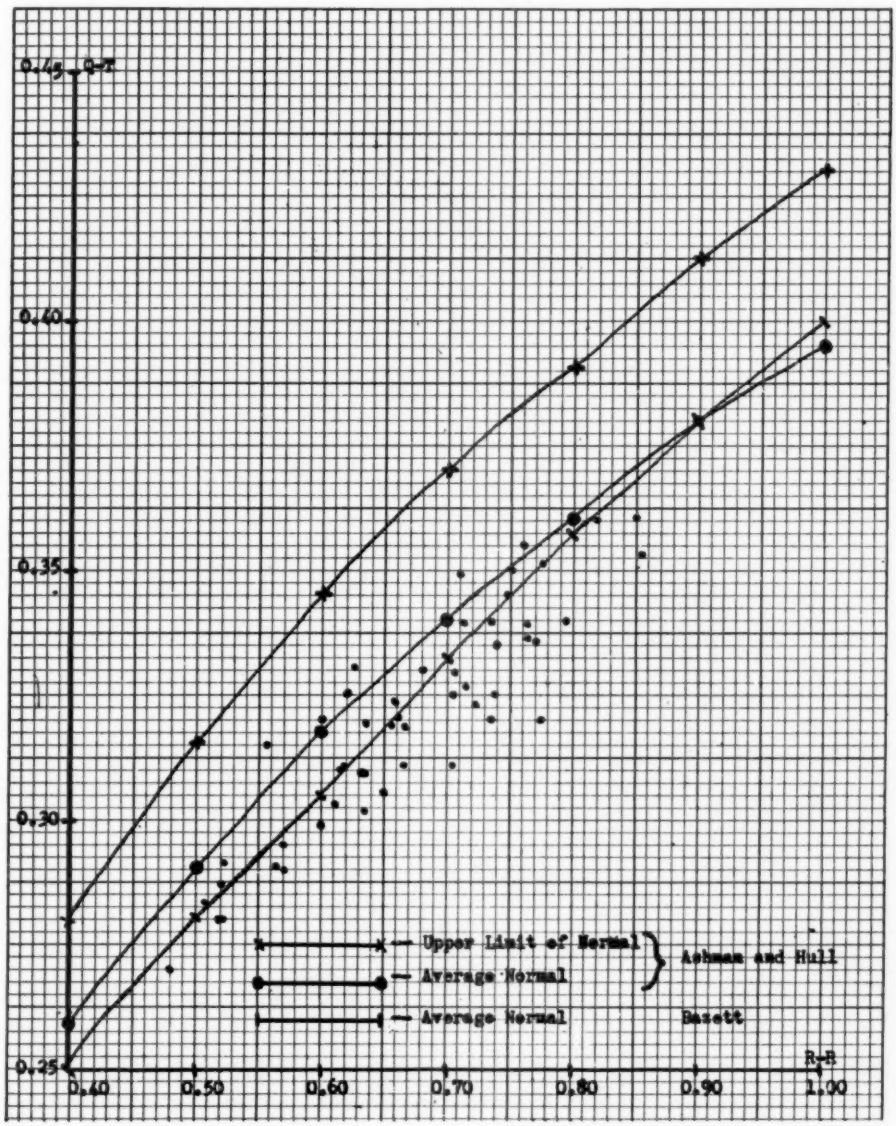

Fig. 1.—Measured Q-T intervals plotted against cycle length in seconds, and normal curves for adult women.

CONCLUSIONS

1. Measurements of the Q-T interval were done on the electrocardiograms of fifty pregnant women.

2. All measurements were found to fall within the normal limits as determined by previous studies done on normal adult women.

3. Making use of Q-Tc (the corrected Q-T interval),[5] furnishes a simple means of determining whether a given measurement is above or below the normal range.

4. All corrected Q-T intervals in this series were below the commonly accepted upper limit of 0.425.

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Clinical Reports

ISOLATED MYOCARDITIS IN NEWBORN AND YOUNG INFANTS

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MYOCARDITIS seems to be more common in children than in adults, even if epidemic diseases are not taken into account. Saphir,[20] for example, reported an incidence of 6.83 per cent in a post-mortem study of 1,420 children, whose ages ranged from 8 days to 16 years. During the same period of observation he found an incidence of 4.05 per cent in a post-mortem study of 3,712 adults.

Myocarditis is not uncommon in infancy, especially subsequent to infectious diseases, such as diphtheria, scarlatina, sepsis, typhus, rheumatic fever, and pneumonia. In all probability, it is more common at this age than has been recognized, because it is difficult to diagnose and, therefore, easily escapes attention unless roentgenograms and electrocardiograms are made routinely in all suspected cases.

In the majority of the cases that have been reported, myocarditis in newborn infants has been part of a general disease and has not been very significant in itself. An example is myocarditis associated with sepsis, emanating generally from the umbilicus or due to congenital syphilis.

Fetal endocarditis attracted much interest in earlier literature, and cases of fetal endomyocarditis also have been observed. These cases have given rise to the assumption that some cases of congenital defects of the heart are of inflammatory origin. Recent studies,[4,10,20] however, have cast doubt upon this view.

Isolated myocarditis, a condition in which the cardiac findings are the only, or at least the dominating feature, seems to appear at any age. Its etiology is unknown. It is frequently difficult to diagnose clinically. It is often unrecognized, except at necropsy, and even then the disease usually is difficult to identify. Macroscopically, the heart is enlarged more or less conspicuously, but there is nothing else remarkable. Furthermore, the majority of pathologists emphasize the fact that a thorough histologic examination using a series of sections is often necessary before the changes can be recognized. In the

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From Norrtull's Hospital and the Pathologic Institute of the Caroline Hospital, Stockholm.

more acute cases these changes consist of infiltration of the interstitial tissue by lymphocytes, plasma cells, leucocytes, and in some places, by eosinophiles. Degeneration of the muscle fibers of varying degrees of severity has also been noticed, and in long-standing cases an increase of the interstitial tissue is present.

Isolated myocarditis has been observed in a few instances among children in infancy. A review of such cases was published recently by Saphir and his associates[20] and by Keller.[15] It seems to be rather rare among newborn infants. Saphir,[20] who bases his opinion on a study of the literature and on the examination of the hearts of newborn babies, asserts that except for myocarditis due to congenital syphilis, fetal or congenital myocarditis is extremely rare, if not nonexistent.

In the literature there are a few case reports of newborn and young infants with myocardial changes that are interpreted as congenital. In no case, however, can the arguments brought forward to support such an interpretation be considered convincing. One case of calcification of the myocardium with slight inflammatory changes was interpreted by Jacobsthal[14] as congenital myocarditis. Opinions differ as to the correctness of Jacobsthal's interpretation, and Hart,[11] among others, asserted that the inflammatory changes observed by Jacobsthal were more probably reactive ones due to the calcification. Iff[13] and Diamond[5] also report cases of calcification of the muscular tissue of the hearts of newborn infants, in which cases the tissue exhibited degenerative changes but no signs of inflammatory processes.

In some cases of myocarditis among children about 6 months old,[9,11] in which congenital genesis was assumed, such a long time had elapsed between birth and death that the findings cannot be considered convincing.

In the last few years paroxysmal tachycardia has been observed rather frequently among newborn and young infants, and one might believe myocarditis to be the provoking cause in some cases, as seems to be the case with older children. Also for that form of the disease in which pre-excitation exists, it has been thought possible that myocarditis can cause the disturbance in rhythm.[3,18] In most cases of paroxysmal tachycardia occurring at this very early age, it has not been possible to recognize any causative heart disease or provoking factor; the hypothesis advanced has been that there may be a defective central and autonomous regulation of the activity of the heart during early infancy. Only in one instance[19] have myocardial changes been detected, and in this case they were localized to the right auricle.

It is also noteworthy that in three cases of auricular flutter in newborn infants, the arrhythmia existed prior to delivery; this was also the case with one instance of auricular fibrillation and paroxysmal tachycardia.

Finally, in the heterogeneous group, idiopathic hypertrophy of the heart, a number of cases are reported with inflammatory changes in the myocardium.[2,16,17] The histologic pictures resembled mild nonspecific pancarditis, and the possibility of an intrauterine infection or toxemia has been suggested. However, none of these infants was under 6 months of age.

Thus, cases of isolated myocarditis and what were believed to be sequelae to intrauterine myocarditis have been found in infants. However, one link in the chain is missing, namely, verified myocarditis in fetuses or newborn infants.

During the last six months we have had the opportunity of studying a number of cases of myocarditis among newborn and very young infants. The cases demonstrate various different types of the course of the disease among infants and show that the disease is in all probability not uncommon and is of practical significance. As we have pointed out, myocarditis is difficult to diagnose, and even though heart disease was established in the majority of our cases, a complete diagnosis was not possible before autopsy or even before a microscopic examination of the heart had been made. Three of the infants showed paroxysmal tachycardia. In none could the etiology of the disease be explained. They must be described as cryptogenic. In two newborn infants the myocarditis was probably congenital, although no proof of such a genesis can be produced.

CASE REPORTS

CASE 1.—(Norrtull's Hospital, F 675/46.) The patient was a 9-day-old girl without any significant family history. The 37-year-old mother was a secundipara and her first child was 4½ years old and healthy. Previously the mother had been generally healthy except for a nontoxic goiter that had never given trouble. While pregnant with our patient she had felt constantly tired and two months before term had been treated for bilateral maxillary sinusitis. She could not remember having had fever. She showed no signs of toxemia due to pregnancy; the blood pressure was normal and there was no albuminuria.*

The delivery was normal. The baby weighed 3.76 grams at birth. During the first few days the child appeared to be healthy and nursed well. Three or four days after birth, however, she began to appear sluggish and to lose her appetite. On the ninth day there was a sudden decline in the health of the infant and after vomiting, she became cyanotic. On examination the rate of the heart was found to be 300 beats per minute. The child was transferred immediately to the Children's Hospital. On her arrival at Norrtull's Hospital, she was in poor condition. She was obviously cyanotic, had cold hands and feet, and had edema localized to the inferior part of the legs and the feet. The liver was palpated three fingerbreadths below the costal margin. On auscultation of the heart no definite murmurs were heard. The electrocardiogram showed what was considered to be a sinus tachycardia with a rate of about 300 per minute and pronounced right-sided preponderance. A radiograph of the heart showed a conspicuous enlargement of the left ventricle without lung stasis. The morning after admission to the hospital, the electrocardiogram showed low voltage complexes and the cyanosis had increased; the child was breathing only with effort. The heart rate was still around 300. During the course of the day she became still worse and appeared to be dying. On admission to the hospital she had been given 0.125 mg. of neostigmine, which had had no effect. Three drops of Digitotal were given three times, which is about equivalent to 7.5 mg. of digitalis folia. A further injection of neostigmine was then administered and return to normal heart rate occurred immediately. The result was a marked clinical improvement. The heart rate fell to 125. The electrocardiogram no longer showed low voltage, but a few extrasystoles were present. Conduction time was normal. The patient continued to improve for ten hours, after which sudden death occurred during the night without any previous signs of its approach.

Post-mortem examination revealed moderate enlargement of the heart, the heart weighing 30 grams (normal weight, 20, or at most, 25 grams). The heart was dilated and flabby. There were no abnormalities in the endocardium or coronary arteries. The myocardium was slightly

*Wassermann reaction was negative.

spotted. The lungs were rather large, hyperemic, and extremely edematous. The spleen weighed 14 grams and the kidneys, 43 grams. The liver was mottled and congested. It weighed 125 grams.

Histologically, there was observed a pronounced interstitial myocarditis (Fig. 1), especially in the left ventricle, but also in the other parts. The myocarditis was characterized by degenerative changes with fatty degeneration and atrophy of the muscular fibers. There was interstitial edema and infiltration mainly by lymphocytes but also by polymorphonuclear cells and a few plasma cells, eosinophiles, and epithelioid cells. There were no vascular changes. Staining for spirochetes by Levaditi's method gave a negative result. The liver and the spleen showed pronounced chronic congestion with central atrophy in the liver lobules.

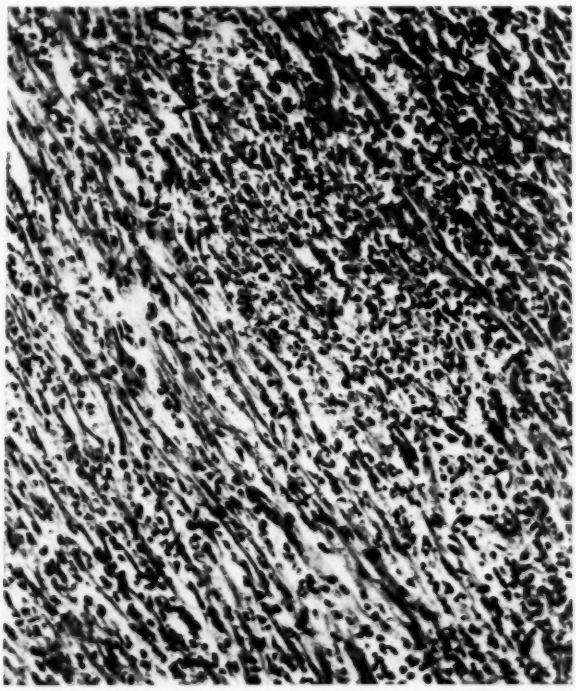

Fig. 1.—Section from myocardium of patient in Case 1 (×120).

CASE 2.—(Crown Princess Lovisa's Hospital, 1256/46.) This case was very similar to Case 1. The infant's parents were healthy. Pregnancy and delivery were normal. The first few days after birth the boy seemed to be healthy, but on the fifth day he became acutely ill with cyanosis and shallow, hasty breathing, for which reason he was transferred to the hospital, where he died shortly after admission. Unfortunately, there is no report of the heart rate, and because of the poor condition of the infant it was impossible to take an electrocardiogram or a roentgenogram.

Post-mortem examination revealed the same pathoanatomic picture as in Case 1. The heart weighed 35 grams. It also displayed mild fibrinous pericarditis. In the left auricle there was a small, partly organized blood clot. The spleen weighed 25 grams; the kidneys, 11 grams; and the liver, 186 grams.

The two following cases originate from the children's wards of country hospitals and were sent in for pathoanatomic examination. With the kind permission of these hospitals, they will be reported briefly.

CASE 3.—(Boden.) The patient was a 3-week-old baby whose illness started with sudden collapse and extreme tachycardia. The infant was admitted to the Children's Department of the hospital, where he died after twenty-four hours. *Histologically*, the heart finding was, on the whole, similar to that of Case 1, but the changes were not so pronounced and were localized to the left ventricle. Etiology was unknown.

CASE 4.—(Norrköping.) The fourth patient was a baby boy who at the age of 2½ months showed evidence of paroxysmal tachycardia. The infant died at the age of 4½ months. A *post-mortem examination* showed that the heart was considerably enlarged, the weight being 60 grams. Microscopic examination in this instance revealed a preponderantly chronic myocardial process with fibrosis, which, judging by appearances, seemed to be of inflammatory genesis without any signs of the scars being caused by changes in the blood vessels.

The myocardial changes in the first two cases do not in themselves give any direct guidance with respect to age. The fairly severe hypertrophy of the heart, the marked stasis and mottling of the liver, and the plainly evident organization of the thrombus in the auricle in the one case furnish, on the other hand, a certain amount of evidence on this point. Nor is it possible to determine the exact age of these changes, but it is not very probable that the hypertrophy of the heart and the high degree of liver stasis, in particular, could have reached such a stage of development if the myocarditis had arisen after birth. Therefore, we have nothing to prove that the myocarditis had been present before birth, but the circumstances at hand are evidence for, rather than against, the assumption that congenital myocarditis was present.

Finally, a case may be mentioned that might well be considered isolated myocarditis in a newborn infant, and with the child surviving the disease.

CASE 5.—(Norrtull's Hospital, F 307/47.) On the first day of life the infant in question, a girl, suffered from repeated attacks of cyanosis and, therefore, was admitted to Norrtull's Hospital. The history contained nothing of interest from the standpoint of heredity. The mother had been healthy during pregnancy and the delivery was normal. On arrival at the hospital, the infant was severely affected. Her face was pale and gray, and she had pronounced dyspnea, without fever. On auscultation of the heart a gallop rhythm was audible. A roentgenogram of the thorax exhibited a conspicuously enlarged heart. Another positive physical finding was an enlarged liver of increased firmness, the lower margin of which extended one fingerbreadth below the costal margin. The child was placed in an oxygen incubator but recovered only slowly. For the first few days she was given penicillin and strong stimulants, without any visible effect. After a week the child began to nurse by herself after previously having been nourished by means of a stomach tube. The gallop rhythm disappeared. The first heart sound was very faint and indistinct, but after another week it recovered its normal tone. It was not until two weeks later that the child could manage without extra oxygen, and after six weeks the weight curve began to rise. After seven weeks the child was discharged from the hospital. Apart from the circulatory signs, no anomalous changes could be detected, and in particular, there were no signs of other infectious processes or intracranial lesions.

During the stay of the patient at the hospital, the volume of the heart varied as shown in Table I.

The child thus began to suffer from severe cyanotic attacks soon after birth and the subsequent serious course of the disease was dominated also by dyspnea. The heart findings were temporary tachycardia with gallop rhythm; there was considerable enlargement of the heart and liver, which organs recovered normal size simultaneously; and there were transient electrocardiographic changes with prolongation of the P-Q and Q-T time, initial flattening and thereafter inversion of the T waves in the standard leads with ultimate recovery.

TABLE I. THE VARYING VOLUME OF THE HEART IN CASE 5

DAY AFTER BIRTH	VOLUME (ML.)	ML. PER KG. OF BODY WEIGHT
Second	67.5	19.3
Sixth	74	20.6
Twenty-second	34	11.6
Thirty-seventh	35	11.3
Sixty-seventh	62	12.8

The electrocardiogram showed changes as given in Table II.

The five cases which have been presented constitute various types and stages of isolated myocarditis among newborn and young infants. Of the five infants, three had paroxysmal tachycardia. Greatest interest is naturally attached to those cases in which myocarditis was probably congenital.

TABLE II. ELECTROCARDIOGRAPHIC CHANGES IN CASE 5

AGE (DAYS)	RATE (PER MIN.)	P-R INTERVAL LEAD II (SEC.)	Q-T INTERVAL LEAD II (SEC.)	T WAVE			ELECTRICAL AXIS
				LEAD I	LEAD II	LEAD III	
2	160	0.12		Isoelectric	Positive	Positive	140°
4	150	0.12	0.22	Isoelectric	Slightly positive	Slightly positive	140°
16	125	0.13	0.30	Negative	Negative	Slightly positive	
23	172	0.14		Isoelectric	Isoelectric	Slightly negative	120°
30	145	0.12		Isoelectric	Isoelectric	Slightly negative	100°
40	130	0.10	0.26	Positive	Positive	Slightly negative	80°
67	160	0.11	0.24	Well-developed		Negative	80°

SUMMARY

Five cases of isolated myocarditis among newborn and young infants are described. Four infants died and were subjected to post-mortem examination. The cases represent various types and stages of the disease. Three of the infants had paroxysmal tachycardia. In two, myocarditis was probably congenital. The cause of the disease could not be explained in any of the cases.

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A DEVICE FOR MEASURING THE MEAN ELECTRICAL AXIS OF THE HEART

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IN 1913 Einthoven, Fahr, and De Waart[1] described a method for determining the manifest value and direction of the mean of the instantaneous electromotive forces produced by the heart throughout the QRS interval. The fundamental principles of the Einthoven equilateral triangle also were set forth in that publication. The vector quantity representing the mean of the instantaneous electromotive forces has been designated the mean electrical axis of the heart. The angle which the mean electrical axis makes with the horizontal, that is, the base of the equilateral triangle or a line representing Lead I, was designated by Einthoven as the angle alpha. A number of methods have been described by which the angle alpha may be determined. These include the chart of Carter, Richter, and Greene[2] and also that devised by Dieuaide.[3] The triaxial reference system developed by Bayley[4] has also proved useful. The accuracy of the Einthoven triangle and that of the assumptions upon which it is based have been questioned, but Wilson[5] has pointed out that the error of this method is negligible so far as its practical applications are concerned.

In order to avoid the use of elaborate charts and to eliminate the need for preparing a separate diagram for each electrocardiogram being interpreted, a device has been prepared for determining the mean electrical axis which is an adaptation of the "Magic Slate."* This slate is marketed as a toy writing board. It consists of a supporting cardboard one of whose surfaces is dyed black and impregnated with a paraffin material. Over this there is a heavy, translucent, glossy paper and overlying this, a clear plastic sheet. When a line is drawn on the plastic sheet with a blunt-pointed, wooden stylus, the impression appears on the glossy sheet as a result of its compression against and adherence to the impregnated black cardboard. This impression is erased simply by lifting and separating the plastic and glossy sheets from the cardboard (Fig. 1). A diagram of the Einthoven triangle circumscribed by a circle graduated in degrees was drawn upon the glossy sheet in India ink. Perpendicular lines to the three sides of the triangle were also inscribed (Fig. 2). In order to use this diagram, the algebraic sum of the areas of the Q, R, and S deflections of any two of the three standard leads is determined and the appropriate number of

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*Manufactured by the Strathmore Company, Aurora, Ill.

spaces is counted on the proper side of the respective lead line. Perpendicular lines are drawn from the points thus determined into the triangle until they intersect. A third line is then drawn from the central point of the triangle, *0*, through this point of intersection and extended to the circle which circumscribes the triangle. That point on the circle intersected by the extended line represents the angle alpha expressed in degrees. The magnitude of the mean electrical axis is represented by the length of the line from the central point *0* to the intersection of the perpendicular lines from the sides of the triangle. The mean electrical axis thus determined is erased by simply separating the glossy sheet from the underlying cardboard and the device is then ready for use again.

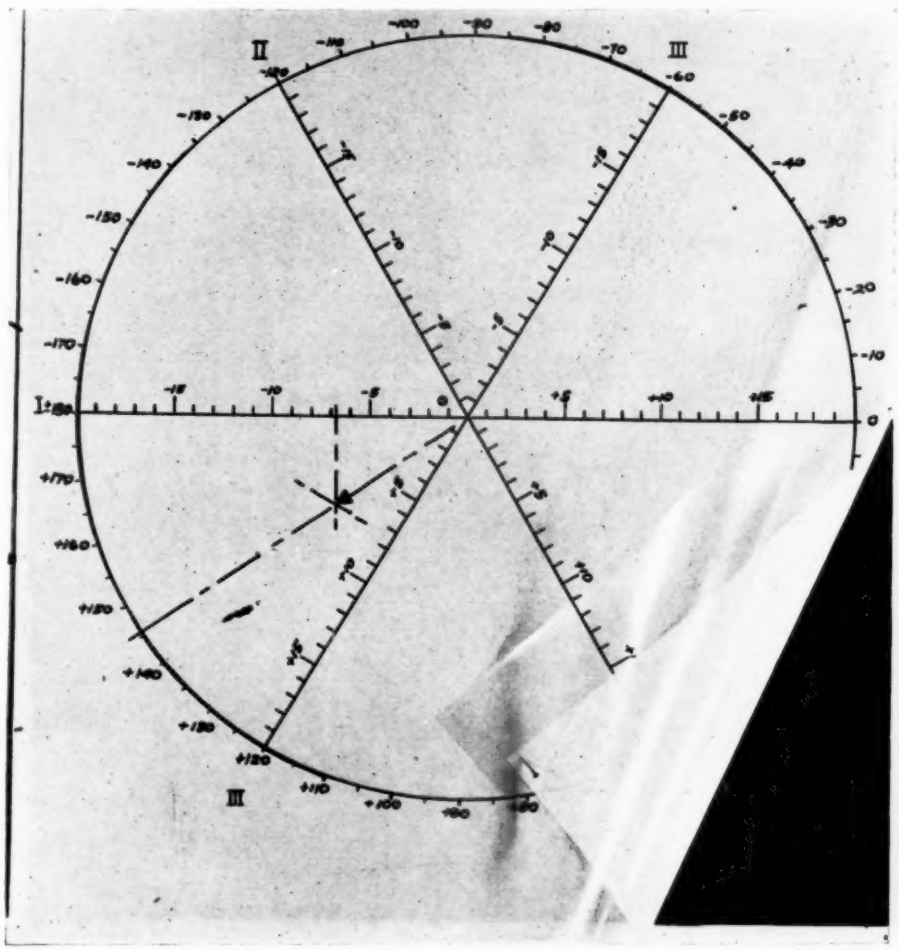
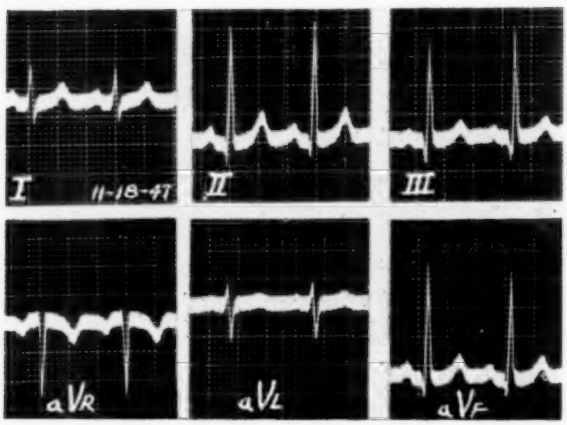
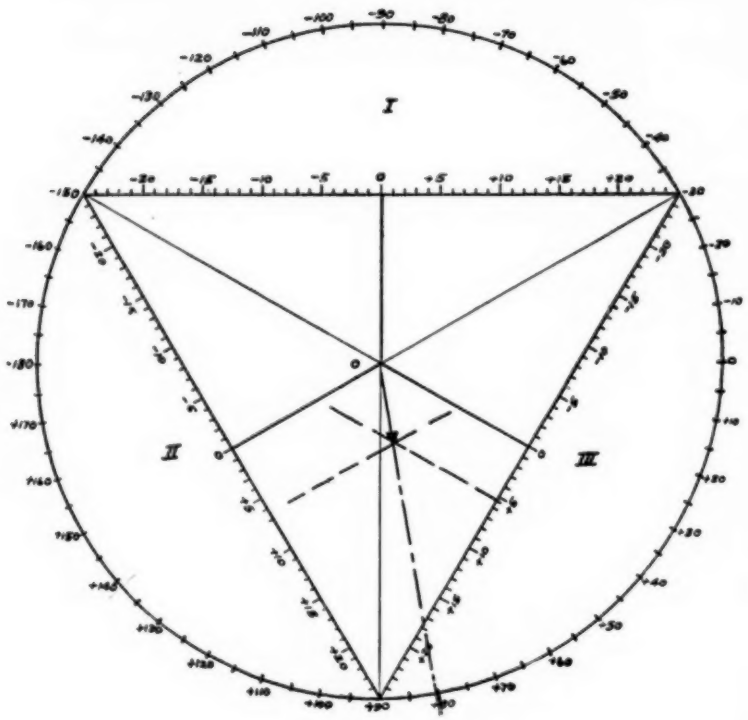


Fig. 1.—Photograph of "Magic Slate" as modified for use in determining the mean electrical axis. The clear plastic sheet, which is uppermost, and the translucent glossy sheet beneath it, have been turned back at the lower right-hand corner to reveal the black, paraffined board backing. In this preparation the tri-axial reference system has been inscribed upon the glossy second sheet. The determination for a case of marked right axis deviation (+146°) is shown. To erase, the clear and the translucent sheets are simply lifted up from the backing.



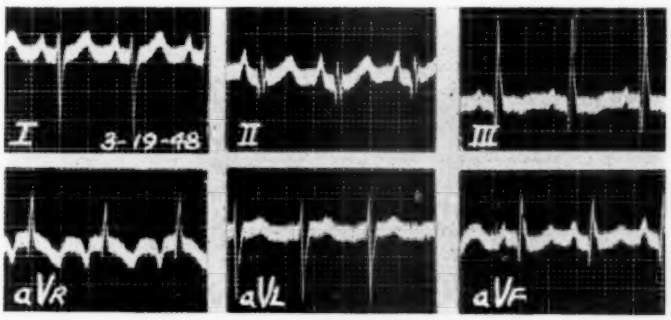
A.



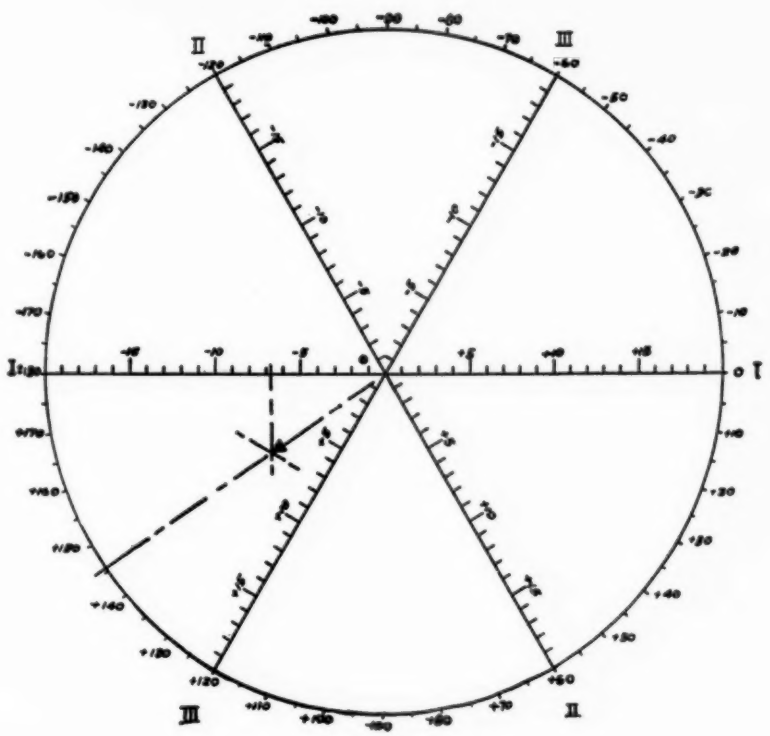
B.

Fig. 2.—*A*, Standard and unipolar limb leads from a 13-year-old girl with possible rheumatic fever. The area of QRS is +14 units in Lead I, +63 units in Lead II, and + 52 units in Lead III.

B, Photograph of mean electrical axis as determined upon the "Magic Slate" preparation with Einthoven triangle inscribed upon the translucent sheet. Mean electrical axis is +81 degrees.



A.



B.

Fig. 3.—*A*, Standard and unipolar limb leads from a 5-year-old boy with the tetralogy of Fallot. The area of QRS is −34.5 units in Lead I and +36 units in Lead III.

B, Photograph of mean electrical axis as determined upon the "Magic Slate" preparation with triaxial reference system inscribed upon the translucent sheet. Mean electrical axis is +146 degrees. Area units have been doubled to facilitate measurements so that −6.9 units have been marked off on the I-I axis and +7.2 units marked off on the III-III axis.

A similar construction using the triaxial reference system of Bayley[4] has also been prepared (Fig. 3). The algebraic sum of the areas of the Q, R, and S deflections in any two of the three standard leads may be determined and applied to the figure along the axis of the proper lead. Perpendicular lines are then drawn from the leads so employed until they intersect. A line is then drawn from the center of the reference system, *0*, through the intersection of the perpendicular lines and extended to intersect the circle. Then, as in the first construction, the angle alpha is simply read, in degrees, at the point of intersection. Examples illustrating the use of both constructions are shown (Figs. 2 and 3). If the electrocardiographic areas are larger than the units designated on the diagram they can be reduced by an appropriate fraction.

The mean electrical axis of the heart is most accurately determined by estimating the electrocardiographic area of each of the elements of the QRS complex rather than by using merely the size of the Q, R, or S deflections in each of the various leads employed. The electrocardiographic areas can be estimated by multiplying the height of each individual deflection by one-half the width of its base, in the manner described by Ashman and Byer.[6]

SUMMARY

A device helpful in determining the mean electrical axis of the heart has been described. It employs the "Magic Slate," which is commercially available as an inexpensive toy.

This device can be used repeatedly and it has greater flexibility than other more elaborate charts now available.

It must be borne in mind that the mean electrical axis of the heart is influenced by several factors other than the relative weights of the two ventricles. Chief among these are the position of the heart and the status of intraventricular conduction.[7]

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Abstracts and Reviews

Selected Abstracts

Wilson, M. G., Payson, J. W., and Lubschez, R.: Experience of Rheumatic Patients Who Served in the Armed Forces, 1942-46. Am. J. Pub. Health **38**:398 (March), 1948.

Of 268 rheumatic patients of military age in the New York Hospital Children's Clinic, 62 per cent (167) were accepted for the Services. One hundred one patients were classified as 4F (physically unfit for military duty). In the Service group, 23 per cent had had one or more attacks of active carditis with failure. In about one-half of the Service group and one-third of the civilian group, the physical signs of valvular lesions had regressed. In the civilian group the past rheumatic history was more severe and the resultant cardiac damage was of greatest degree. In this group 43 per cent had had one or more attacks of active carditis with failure during childhood.

The incidence of rheumatic fever among the patients in military service revealed that three men were hospitalized for rheumatic fever while in the Armed Forces. In the civilian group during 402 patient-years, there were seven patients with recurrent attacks, one of whom died. In addition, two patients had bacterial endocarditis and two developed auricular fibrillation. It is noteworthy that cardiac failure, bacterial endocarditis, and auricular fibrillation did not occur among the men in the Service. Of particular importance is the observation that among the men who returned to the clinic after discharge, no change in physical signs or cardiac enlargement was observed. The authors state that in their experience the risk of a recurrent attack of rheumatic fever is no greater while in the Services than while in civilian pursuits.

BELLET.

Rabinovitch, R., Elliott, K. A. C., and McEachern, D.: Cytochrome C: Intravenous Administration in Man. J. Lab. & Clin. Med. **33**:294 (March), 1948.

Cytochrome C was administered intravenously in doses of 50 to 512 mg. daily for periods up to thirty-one days. Subjects included one normal individual and eight patients with various diseases. The concentration was determined by the spectrophotometric method described by Rosenthal and Drabkin.

Injections of 50 to 500 mg. of cytochrome C, administered intravenously at intervals of one week to the one normal adult, and single doses of 500 mg., administered to two patients suffering from neuromuscular disease, caused no subjective symptoms. No changes were noted in pulse, respiration, blood pressure, temperature, or basal metabolism for three hours following injection.

Eight patients suffering from various neuromuscular disease and one normal control were given daily intravenous doses of cytochrome C which varied from 50 to 500 milligrams. No detectable changes in symptoms or signs were produced. The substance was not detected spectroscopically in the serum of these patients except where blood samples were collected within thirty minutes after injection of single doses of 500 milligrams.

KLINE.

Green, D. M., Johnson, A. D., Lobb, A., and Cusick, G.: The Effects of Adrenalin in Normal and Hypertensive Patients in Relation to the Mechanism of Sustained Pressure Elevations. J. Lab. & Clin. Med. **33**:332 (March), 1948.

Eighty continuous infusions of adrenalin in a concentration of 1.0 mg. per cent were administered to thirty-nine men and twelve women whose blood pressures ranged from 90 to 246 systolic and from 55 to 126 diastolic. During the administration of saline, pulse rate and blood pressure values were determined before, during, and for twelve hours after each infusion. When the undiluted solution reached the circulation, the systolic and occasionally the diastolic pressure rose above the preinfusion value. An increase in the rate of administration produced a further rise in systolic and diastolic pressures to a new maximum in one to three minutes. Following cessation of infusion, both systolic and diastolic pressures dropped abruptly. A minimum level was reached usually by ten and not later than fifteen minutes after clamping of the infusion tubing. These minimum levels were lower than the initial blood pressure levels in all but one instance and were accompanied by cardiac acceleration. Daily infusion on the same subject produced almost identical blood pressure responses. However, increase in the subjective limit of tolerance was marked.

The authors found that in general the higher the patient's initial pressure the farther the pressure dropped below the initial level when the infusion was stopped. In a number of instances the minimum pressures developed within the range usually associated with shock. The depression of pressure in association with evidences of vasodilatation suggests a temporary persistence of compensatory vasodepressor activity, either nervous or humoral.

It was found that the tolerance to adrenalin was inversely proportional to the initial blood pressure. One subject in the series complained of mild substernal pain which subsided without sequelae when the infusion was stopped. Cardiac irregularity, due to premature contractions, occurred to some degree in nearly all patients. In one instance it was sufficiently marked to dictate the cessation of the infusion. Three persons developed cerebral symptoms, characterized in one by intense headache and momentary syncope, in another by transient unconsciousness, and in a third by a hemiplegic syndrome without loss of consciousness, from which recovery was complete in twelve hours. These alarming episodes which occurred during the latter phase of these studies influenced their termination.

The correlation between the height of the initial pressure and the depth of the subsequent postinfusion depression provides additional data to indicate that the vasodilator capacity of the hypertensive individual is enhanced rather than diminished. The accumulated evidence demonstrates the availability of compensatory mechanisms in the hypertensive subject and the capacity of the vascular apparatus to respond effectively when these mechanisms are properly stimulated.

KLINE.

Selzer, A.: The Immediate Sequelae of Myocardial Infarction. Their Relation to the Prognosis. Am. J. M. Sc. **216**:172 (Aug.), 1948.

A series of 130 unselected cases of recent myocardial infarction found at autopsy was examined. In thirty-five patients, myocardial infarction was a terminal event in otherwise seriously ill patients and was regarded as of little clinical interest. The remaining ninety-five patients were apparently well prior to the onset of the myocardial infarction and were subjected to detailed analysis as "primary" myocardial infarction.

The immediate cause of death in this group of ninety-five cases was: progressive circulatory failure, with or without shock, in twenty-eight cases; sudden death due to arrhythmia in twenty-four cases; embolic phenomena in fifteen; cardiac rupture in eight; and secondary coronary thrombosis in five cases. In the remaining fifteen cases death was due to incidental complications not related to myocardial infarction.

No significant correlation was found between the age of the patients, the degree of the coronary arteriosclerosis, the size of the infarction, and the presence of myocardial scars and of cardiac hypertrophy, on one hand, and the course, the duration of illness, and the frequency of complications, on the other hand. This is interpreted as indicating the adequacy of circulatory adjustment even in cases with extensive damage to the heart.

The prognosis of acute myocardial infarction is unpredictable because the importance of cardiac insufficiency, the direct consequence of the damage to the myocardium, is outweighed by secondary complications. The number of patients who die immediately is twice, or perhaps three times greater than the estimated number of patients who develop irreparable cardiac damage. The important sequelae of myocardial infarction, which can be considered potentially preventable causes of death, are serious arrhythmia, thromboembolic phenomena, and shock.

DURANT.

Flaxman, N.: Digitoxin Poisoning. Report of 30 cases. Am. J. M. Sc. **216:**179 (Aug.), 1948.

In thirteen months digitoxin poisoning was seen in thirty patients who had received the regularly prescribed doses of this isolated digitalis glycoside. The age and sex of the patient or the type of underlying heart disease had no relation to the occurrence of the poisoning. Symptoms, such as are known to be due to digitalis overdosage, occurred infrequently in these patients. Signs of disorders of the cardiac mechanism, especially the more serious conduction disturbances, were the earliest and most frequent clinical and electrocardiographic manifestations.

Considerable caution should be exercised in the administration of the digitoxin preparations in the regularly advised dosage and form to any patient suffering with congestive heart failure, because the action may be rapidly intoxicating to the cardiac musculature and its conduction system. The factor of safety for this particular digitalis purpurea glycoside seems to be extremely narrow.

DURANT.

DeMuth, W. E., and Rawson, A. J.: Pseudomonas Septicemia and Endocarditis. Report of a Case. Am. J. M. Sc. **216:**195 (Aug.), 1948.

A case is reported of protracted sepsis by *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) with lesions in many organs and massive acute endocarditis involving the aortic valve. Only one other case of endocarditis of the aortic valve caused by this organism has been found in the literature.

DURANT.

Thompson, J. L., Jr., and Kistin, A. D.: Hoarseness in Heart Disease. Ann. Int. Med. **29:**259 (Aug.), 1948.

Two cases of rheumatic heart disease associated with left recurrent laryngeal nerve paralysis are reported. In one, a 30-year-old man who died following an attack of acute rheumatic fever, necropsy showed minimal scarring of the mitral valve and only slight enlargement of the left auricle. The other was a 31-year-old man in whom angiocardiographic studies revealed considerable enlargement of the left auricle. Common to both cases was dilatation of the pulmonary artery. Because of the peculiar anatomical relations between the left recurrent laryngeal nerve and the pulmonary artery and aorta, the dilatation of the pulmonary artery was considered to be responsible for the left vocal cord paralysis noted in the two cases. The authors also suggest that there may be another but unknown factor contributing to the left recurrent laryngeal nerve paralysis in view of the large number of cases with comparable dilatation of the pulmonary artery which do not exhibit pressure effects upon the nerve. The many reports dealing with the subject of recurrent laryngeal nerve paralysis in heart disease are also reviewed and analyzed.

WENDKOS.

Altshuler, S. S., Hoffman, K. M. and Fitzgerald, P. J.: Electrocardiographic Changes in Diphtheria. Ann. Int. Med. **29:**294 (Aug.), 1948.

In the American Zone of Germany, 600 patients with proved diphtheria were seen from September, 1945, to December, 1946. This number included twenty-six cases of cutaneous diphtheria. The youngest patient was 18 years of age, the oldest was 43, and the average age was 23.4 years. An electrocardiogram was recorded as soon as diphtheria was suspected clinically or when a positive culture was reported. Thereafter, electrocardiograms were recorded at weekly intervals or more often when indicated.

Of the 600 cases of diphtheria studied, 143 (23.9 per cent) presented electrocardiographic changes at some time during hospitalization. Flattening or inversion of the T waves occurred in 108 cases. In over 50 per cent of this number, the T-wave abnormalities were present in three or more leads. T-wave abnormalities persisted for from two, to longer than twenty-three weeks.

Two patients developed right bundle branch block. Deep inversion of all the T waves followed the temporary bundle branch block pattern. The electrocardiogram was not within normal limits after eighteen weeks in one of these patients, nor after twenty-three weeks in the other patient. Prolongation of the P-R interval occurred in eleven patients. The commonly held opinion that prolongation of the P-R interval is the most common abnormality in diphtheritic infections was not substantiated by this study. Two patients developed complete heart block without a preliminary period of lesser degrees of A-V heart block. Of these two patients with complete A-V heart block, the electrocardiogram in one returned to normal after six weeks, whereas it returned to normal after ten weeks in the other patient. Recovery was uneventful in both cases.

The study of these 600 patients permits the general observation that if a patient with diphtheria has not shown electrocardiographic changes by the end of the fourth week after the onset of his clinical infection, the possibilities of myocardial involvement from the disease are few.

No correlation was possible between the severity of the infection and the severity of the electrocardiographic changes. The patients with the most marked and prolonged abnormalities usually had clinically severe infections but some patients with mild infections who were asymptomatic after the first few days had marked and persistent electrocardiographic changes.

WENDKOS.

Sweeney, J. S., and Pace, J. M.: Hypertension Caused by Unilateral Kidney Disease (A Follow-Up Report). Ann. Int. Med. **29**:370 (Aug.), 1948.

Twelve days following the removal, in a 21-year-old woman, of a diseased shrunken right kidney due to antecedent pyelonephritis, the systolic blood pressure level fell from 240 mm. to 126 mm., the diastolic blood pressure level fell from 140 mm. to 78 mm., and the hypertensive papilledema receded completely. Seven years following the operation, the systolic blood pressure averaged 118 mm. and the diastolic pressure 82 millimeters. The patient in all respects appeared to be normal. The authors consider these findings to be conclusive evidence that an occasional case of severe hypertensive disease may be benefited by removal of a diseased unilateral kidney.

WENDKOS.

White, J. C., Heroy, W. W., and Goodman, E. N.: Causalgia Following Gunshot Injuries of Nerves. Ann. Surg. **128**:161 (Aug.), 1948.

The authors present a study of thirteen patients suffering from causalgia as a result of gunshot injuries of nerves. It is their opinion that this term should be limited to include only the sequelae to penetrating wounds of the extremities which cause injury to the nerve trunks and the triad of burning pain, trophic changes, and autonomic phenomena. They also call attention to the fact that vasodilatation is certainly not a constant finding in this clinical entity, although it is possible that this sign is present early in the disease.

The authors noted that the pain in causalgia is aggravated to an unbearable degree by factors which increase sympathetic discharge from the hypothalamic centers, such as thermal and psychic stimuli. Therefore, interruption of the sympathetic outflow, as by preganglionic sympathectomy, is an effective method of treatment and should be performed at an early date. In the authors' cases sympathectomy resulted in consistent relief of the burning pain. It was their impression that this procedure resulted in elimination of efferent sympathetic discharge from the hypothalamic centers rather than in any interruption of pain fibers. The recent work on animals, suggesting that there may be a short-circuiting effect in the area of the injured peripheral nerve which permits direct irritation of sensory afferent fibers by efferent sympathetic impulses, is presented in support of their view.

ABRAMSON.

Keeley, J. L.: Saddle Embolus of the Aorta: Report of Successful Embolectomy. Ann. Surg. **128:257** (Aug.), 1948.

The author reports an additional successful embolectomy at the bifurcation of the aorta. This occurred in a woman 52 years of age recovering from congestive heart failure and also suffering from auricular fibrillation. The diagnosis was made on the basis of sudden onset of paralysis of both feet, severe pain, coldness, and numbness. Pulsations in the abdominal aorta could be felt, but none were present below the level of the sacral promontory. Embolectomy was performed six hours after the onset of symptoms. An obstructing mass of clot was removed from the region of the bifurcation, together with a tail thrombus about six inches long from the right iliac artery and a segment from the left. Immediately after operation, pulsations could be felt in all peripheral arteries except the left dorsalis pedis. Subsequently this vessel also developed pulsations. The only aftereffects were edema of the left leg, which lasted for six weeks, and some persistent weakness of the left peroneal muscles.

With regard to diagnosis, two general types of histories have been obtained in proved cases. One is characterized by sudden localized pain, indicating approximately the point at which the embolus has been arrested, and, after an interval lasting up to several hours, a diffuse type of aching pain throughout the portions distal to the obstruction. The latter is due principally to anoxia of the muscle. This clinical picture can be explained on the basis of occlusion of the main artery accompanied by vasospasm of vessels distally, with subsequent thrombus formation blocking the collateral circulation. The other mode of onset consists of paresthesia as the initial symptom, followed by numbness, diffuse pain, and paralysis as anoxia becomes more severe.

Although the absence of pulsations is the most important sign, this finding should be carefully evaluated. Vasospasm may be so severe as to obliterate pulsations in vessels not obstructed by clot. On the other hand, the presence of pulsations may be deceiving, since there may be transmission of pulsations by a tail thrombus. Theoretically, this should produce a linear thrust (Nordentoft's sign) instead of the normal expansile type of pulsation, but this distinction may be difficult in the presence of much subcutaneous tissue. Tenderness at the site of embolus is not present early, but depends on the development of inflammatory changes in the intima. Pallor occurs early, and later, mottled cyanosis. "Marbled" blanching generally means complete arterial obstruction which will not respond to antispasmodic drugs or blocking of the sympathetic fibers. Late manifestations include motor or sensory paralysis as ischemia produces physiologic interruption of nerve and muscle function.

Differential diagnosis from thrombosis of the aorta is not difficult, since in the latter there is a gradual onset of symptoms related to the slow development of a reduction in peripheral circulation. However, in cases of thrombosis the circulation may become inadequate rather suddenly and the onset of pain and evidences of circulatory inadequacy may therefore appear to be an acute and recent process. The history will, however, differentiate this type of case from aortic embolism.

According to the author, embolectomy is the only life-saving treatment for a patient with an aortic embolus. He points out that almost invariably failure to restore the circulation results in death from gangrene. The general condition of the patient is the deciding factor as to whether to use the transabdominal approach or the indirect approach through the femoral vessels.

ABRAMSON.

Gomez, G. E.: Question of Cardiac Hypertrophy in Residents of High Altitudes. J. A. M. A. **137:1297** (Aug. 7), 1948.

Gomez presents a statistical study of cardiac size of 638 residents of Bogota, Colombia, in an attempt to determine whether existence at the altitude of Bogota (8,016 feet above sea level) is associated with demonstrable cardiac enlargement. Two groups of subjects were studied. The first group, numbering 480, consisted of 182 medical students between the ages of 17 and 30 years, who had lived in Bogota for two or more years, and 298 normal persons of both sexes between the ages of 17 and 50, some of whom were natives of the city and others of whom were recent arrivals. The second group, numbering 158, was composed of seventy-seven soldiers with

a minimum service of six months in the army and a residence in Bogota of two years, and eighty-one soldiers with six months' service in places close to sea level who had come to Bogota only twelve days previously.

Teleroentgenograms in moderate inspiration were taken of each subject and the transverse-diameter of the cardiac silhouette was determined. The height and weight of each subject were measured.

Statistical analysis of the transverse diameters, correlated with the heights and weights of the nonmilitary group of 480 subjects, produced results identical with those which had previously been obtained by Ungerleider and Clark in a study of 1,460 normal persons living at altitudes close to sea level. The authors conclude, therefore, that residence at an altitude of 8,016 feet above sea level does not bring about demonstrable cardiac enlargement.

Similar analysis of the findings in the military group showed evidence of slight cardiac enlargement. Inasmuch as the values for those soldiers who had been in Bogota for some time were identical with those who had only recently arrived at the higher altitude, the authors believe that the slight increase in heart size in the military group is probably a result of the rigorous physical training to which the soldiers are subjected.

HANNO.

McGee, C. J., Priest, W. S., and Kenney, D.: Subacute Bacterial Endocarditis Due to Hemophilus Parainfluenzae. J. A. M. A. **137**:1315 (Aug. 7), 1948.

An 8-year-old boy with rheumatic heart disease developed a subacute bacterial endocarditis complicated by a left hemiplegia, evidently embolic in nature. Early in the illness *Streptococcus viridans* had been reported in blood cultures and a course of sulfathiazole had been given over a period of six weeks without effect. Nine weeks after the onset of the illness, penicillin was administered in a dosage of 500,000 units daily by continuous intravenous drip, and repeated blood cultures showed the presence of *Hemophilus parainfluenzae*. The blood cultures remained positive with penicillin therapy, and in vitro studies showed that the organism was not inhibited by any concentration of penicillin, but was inhibited by a sulfonamide concentration of 3.0 mg. per cent. Penicillin therapy was continued and, in addition, sulfamerazine was administered in a dosage which maintained the blood level between 8.0 and 12.0 mg. per cent. The combined treatment was continued for fifty-two days, following which sulfamerazine alone was given for thirteen days. The blood culture became negative within twenty-four hours after the combined treatment was begun and remained negative on repeated determinations during the course of therapy and after treatment was discontinued. The patient recovered and has remained well during a two-year follow-up. The only residua of the hemiplegia are slight flexion contractures of the left thumb and index finger.

In attempting to explain why a combination of penicillin and a sulfonamide effected a cure when a sulfonamide alone did not, the authors advance the theory that penicillin, which has been shown to penetrate fibrin, somehow enabled the sulfonamide drug to penetrate the fibrin barrier of the valvular vegetations.

The case reported represents the first recovery of a patient with subacute bacterial endocarditis due to *H. parainfluenzae*. Each of the forty cases previously reported in the literature terminated in death.

HANNO.

Brozek, J., Chapman, C. B., and Keys, A.: Drastic Food Restriction: Effect on Cardiovascular Dynamics in Normotensive and Hypertensive Conditions. J. A. M. A. **137**:1569 (Aug. 28), 1948.

The authors review the cardiovascular effects of drastic food restriction and recovery from semistarvation which were noted experimentally in a controlled study on normotensive subjects and which were observed in segments of the European population during World War II, as described in the recent European literature.

In the experimental study, thirty-four normal young men were placed on a restricted dietary intake of 1,600 calories and 49 grams of protein daily for a period of six months. No attempt at sodium limitation was made. The average body weight fell 23.9 per cent; the mean systolic blood pressure fell 11.1 per cent; the mean diastolic pressure fell 7.73 per cent; the mean pulse rate decreased to 37; the average basal metabolic rate decreased to minus 39.9 per cent; and a striking decrease in heart size was noted. At no time during the semistarvation period was circulatory failure observed, although edema appeared uniformly. Controlled rehabilitation in thirty-two subjects was instituted for a period of twelve weeks with a diet of 2,449 calories and 72.85 grams of protein per day. During this period the systolic and diastolic pressures rose slowly to levels slightly below the prestarvation readings. In a group of nineteen subjects, after thirty-three weeks of dietary rehabilitation, the average systolic and diastolic pressures were found to be slightly higher than the original levels, but in the seven subjects who were examined fifty-eight weeks after the end of the strict dietary limitation, the average blood pressure had returned to prestarvation values. In twelve of the men it was observed that a large increase in the caloric intake following the twelfth week of rehabilitation was associated with a rise of both the systolic and diastolic pressures to values slightly above the control values and a rise in the average venous blood pressure. Concomitantly, a moderate tachycardia and exertional dyspnea appeared. One subject, who began to consume from 7,000 to 10,000 calories a day following the twelve weeks of controlled rehabilitation, developed mild congestive failure which responded to dietary restriction, fluid limitation, the administration of ammonium chloride, and bed rest.

The experience of various European observers during the recent war years has shown that conditions of undernourishment, as pertained to prisoners of war, concentration camp inmates, and the general population of the war-devastated counties, brought about decreases in blood pressure and pulse rate in both normal and hypertensive subjects. During recovery from semistarvation, not only does the blood pressure return to normal levels but may also overshoot the mark to reach frankly hypertensive levels.

Of particular interest are the extensive observations made in Leningrad before the outbreak of the war, during the siege period of severe dietary limitation, and during the period following the partial lifting of the siege. During the period of reduced food intake, the incidence of hypertension decreased and in a large number of hypertensive patients reduction of blood pressure to normal or near normal levels occurred. There was, in addition, a definite decrease in the incidence and intensity of symptoms commonly associated with hypertension; angina pectoris and myocardial infarction were encountered less commonly than before the war. Following the end of the siege when the food supply became more plentiful, the incidence of hypertension reached epidemic proportions and the incidence of cardiac insufficiency in hypertensive patients increased. The impression was gained that in some hypertensive patients the disease became much more severe in the poststarvation period than it had been in the presiege period. Frank neuroretinitis and retinal hemorrhages and exudates were observed in a larger number of hypertensive patients than in the prestarvation period, but, interestingly, the incidence of associated renal changes decreased, while malignant nephrosclerosis virtually disappeared.

The results of the European experiences and of the authors' controlled study indicate quite definitely that drastic dietary restriction causes a fall in blood pressure in most normal persons and hypertensive patients. It would seem that the primary causative factor is the caloric limitation. Salt intake was not specifically limited in any of the groups observed, and even if some decrease in sodium intake were present, it was not comparable to the extremely low levels of the Kempner "rice-diet" regimen.

The authors conclude that a diet causing moderate weight reduction is therapeutically indicated in the management of hypertension and that a stringent program of the Kempner type may well be utilized in the treatment of the more severe cases. They warn, however, that in selecting cases for treatment by severe dietary limitation the risk of the patient's becoming worse than before, if he abandons the program, must be kept in mind.

HANNO.

Lampson, R. S., Schaeffer, W. C., and Lincoln, J. R.: Acute Circulatory Arrest From Ventricular Fibrillation for Twenty-Seven Minutes With Complete Recovery. J. A. M. A. **137**:1575 (Aug. 28), 1948.

The authors report the case of a 7-year-old boy who developed sudden circulatory arrest following completion of operative repair of a deep laceration of the foot. The surgical procedure lasted about 75 minutes and was done under open drop ether with cyclopropane induction.

The patient's condition during the operation was good, but after the administration of the anesthesia had been discontinued, the pulse abruptly stopped, spontaneous respiration ceased, and ashen pallor became evident. No heart sounds could be heard on auscultation. Within two and one-half to three minutes following the onset of the circulatory arrest, an incision was made in the left fifth intercostal space directly into the left pleural cavity. The heart was soft to the palpating fingers of the surgeon, and visual observation showed the fine ripples of fibrillation in the left ventricular musculature. Rhythmic cardiac massage was immediately instituted by intermittent compression of the heart against the sternum at a rate of about 60 per minute, and pulsations were then noted at the wrist. At the same time, respiration was maintained by rhythmic compression of the breathing bag containing oxygen. The patient's general appearance began to improve. Fifteen minutes later, when the heart still was not beating spontaneously, 3.0 c.c. of a 1 per cent solution of procaine hydrochloride was given intravenously, and blood transfusion was started. At about this time spontaneous respirations returned. A second dose of 2.0 c.c. of 1 per cent procaine hydrochloride was administered by vein about twenty-six and one-half minutes after the onset of the circulatory arrest, and some thirty seconds later the heart began to stiffen and irregular spontaneous contractions set in. Two minutes later a normal rhythm with strong pulsations supervened.

An electrocardiographic tracing begun before spontaneous contractions of the heart had set in revealed the characteristic findings of ventricular fibrillation, the bizarre ventricular complexes occurring at a rate of about 365 per minute. This was followed by a short period where no evidence of cardiac activity was present, following which a run of ten aberrant arrhythmic ventricular contractions, some preceded by P waves, occurred. A normal sinus rhythm supervened, the QRS complexes being bizarre and of small amplitude and the S-T interval somewhat depressed for a few seconds. The chest wound was closed after penicillin and procaine hydrochloride had been flushed over the pericardium, and the patient was placed in an oxygen tent. Convalescence was complicated by evidences of temporary cerebral dysfunction as a result of the cerebral anoxia, but gradual and complete recovery took place, and the patient was discharged on the twenty-sixth postoperative day. Several electrocardiograms taken during convalescence were within normal limits.

The authors emphasize that the proper measures must be promptly taken when acute circulatory arrest sets in if certain death is to be averted. Because of the rapid development of cerebral anoxemia, complete recovery is not to be expected unless the circulatory arrest has been corrected within three minutes, and survival is unlikely if the elapsed time is more than eight minutes. They point out that the catastrophe is most likely to occur during light anesthesia, in either the induction or recovery phases, when the myocardium is hyperirritable, and that circulatory arrest may be due to either cardiac standstill or ventricular fibrillation. In either case, the circulation must be promptly restored by direct rhythmic cardiac massage and respiration must be artificially maintained with high concentrations of oxygen. Further treatment is then dictated by the type of cardiac disorder present. If ventricular fibrillation is the cause of the circulatory arrest, as evidenced by the direct observation of fibrillatory ripples or by the characteristic electrocardiographic findings, 5.0 to 10 c.c. of a 1 per cent solution of procaine hydrochloride should be administered intravenously or directly into the heart to reduce myocardial irritability. If defibrillation does not occur, the dose may be repeated or electrical stimulation, as used by Beck, can be resorted to if the equipment is available. Epinephrine hydrochloride is contraindicated in the presence of ventricular fibrillation because it makes an irritable myocardium even more irritable. Following the restoration of a normal rhythm, however, epinephrine may be of value in strengthening the contraction of the heart. If the cause of the circulatory arrest is cardiac standstill, as shown by a visibly quiet heart or by the absence of any evidence of activity

electrocardiographically, epinephrine, in a dose not exceeding 1.0 c.c. of a 1:1,000 dilution, may be administered intravenously, into the myocardium, or directly into the heart. An excess of epinephrine may throw a heart in standstill into ventricular fibrillation. If shock and hemorrhage are present, transfusion is indicated in order to insure adequate cardiac filling.

HANNO.

Cohen, H., and Harrison, C. V.: Temporal Arteritis: A Report of Three Cases. J. Clin. Path. **1**:212 (Aug.), 1948.

The cases reported in this paper were all of men, though in previously recorded cases there have been slightly more women than men. The duration of the disease in these three cases was fifteen, eight, and twenty-three weeks, which is shorter than average.

In this series Case 1 recovered completely. Case 3 also recovered, but was left with blindness in his left eye. Case 2 died from myocardial infarction six months after discharge. In Case 1 the lesion appeared to be limited to the temporal arteries, in Case 2 the right circumflex artery was involved, and in Case 3 there was blindness in the left eye due to thrombosis of the central retinal artery.

That the disease is not a localized process is suggested by the frequent occurrence of pyrexia and pains in body and limbs and by a degree of systemic illness out of proportion to the physical findings. The outstanding symptom in all three cases, and in all recorded cases, has been pain in the head, which is usually resistant to analgesics. Removal of a segment of the affected temporal artery for biopsy was certainly of value in relieving symptoms in these cases. It has been suggested that this is due to the interruption of the accompanying nerves.

Nothing is known of the etiology of the disease, and though many of the clinical features suggest an infective cause, so far all attenpts to isolate an organism have been fruitless. Nevertheless, the disease presents a uniform pattern which differentiates it from polyarteritis nodosa or Buerger's disease.

BELLET

Frankland, A. W.: Embolism After Penicillin-Oil-Beeswax. J. Clin. Path. **1**:244, (Aug.), 1948.

The author was able to find only one previously published account of oil embolism following the use of penicillin in an oil-wax medium. In the case described in this report, a mild immediate reaction occurred after an injection of penicillin in oil-wax; the reaction was apparently due to oil embolism.

A 30-year-old woman with ulcerative colitis was given an injection of 600,000 units in 2.0 ml. of calcium penicillin suspended in peanut oil with 4.8 per cent beeswax. The nurse who gave the injection was not sure that the usual precautions of making sure the needle was not in a vein had been carried out. Immediately after the injection the patient felt quite faint; however, five minutes later she said she was feeling quite well. A specimen of sputum was collected the following day. No precautions were taken to make sure that this was not contaminated with any oil or fat from a food source. A further specimen of sputum was taken three days later; however, only in the specimen taken the first day after the penicillin injection and only in certain parts of the field could many oil globules be seen; all these were extracellular and most of them were very minute. Examination of a slide containing stained sputum, and also slides containing unstained and stained penicillin in oil-wax, showed that in no case was there rotation of the plane of polarized light. It is suggested, therefore, that the oil in the sputum had as its source the penicillin oil-wax injection given into the buttock.

BELLET.

Smull, K., Wissler, R. W., and Watson, J. M.: The Effect of Sodium Salicylate Upon Serum Disease in Rabbits. J. Lab. & Clin. Med. **33**:936 (Aug.), 1948.

Using rabbits, the authors tested the influence of sodium salicylate therapy upon the lesions resulting from the injection of large intravenous doses of normal horse serum. Twelve rabbits received two intravenous injections of sterile normal horse serum fifteen to sixteen days apart,

while twelve similarly treated rabbits received large doses of sodium salicylate starting six days after the first injection of horse serum. The drug was administered in quantities designed to maintain an average of about 250 gamma per milliliter throughout each twenty-four hour period. Sedimentation rates and blood salicylate levels were followed.

Normal sedimentation rates persisted in the salicylate-treated animals which did not receive intravenous horse serum. Most of the animals given horse serum showed an increase in the rate above 20 mm. after the first or second injection. Salicylate therapy did not exert any notable effect on the sedimentation rate in spite of the fact that the lesions were less severe in this group of animals. Sustained hypertension was not noted in any of the animals, even in those which developed marked generalized arteritis. In the salicylate-treated animals it was found that levels of 350 gamma per milliliter could not be maintained without producing intoxication and death.

Despite the small series, the results suggest that salicylate treatment had depressed the developing arteritis in the treated group. In the salicylate-treated rabbits the authors found a moderate depression in the concentration of circulating antibody to horse serum which occurred eighteen to twenty-two days after the first injection of horse serum.

Microscopically, the arteritis, when present, usually was seen in the myocardium, lungs, pancreas, mesentery, stomach, kidneys, liver, adrenals, diaphragm, and testes or uterus. Most of the valvular changes were proliferative in type and were found predominantly at the base of the valve leaflets and were confined almost entirely to the mitral and aortic valves as they are in rheumatic fever.

The authors stress that at present one must be cautious in assuming that the inhibitory effect of salicylates upon the lesions of rabbit serum disease can be applied to the lesions of rheumatic fever.

KLINE.

Green, R. S., Iglauer, A., and McGuire, J.: Alterations of Radial or Brachial Intra-Arterial Blood Pressure and of the Electrocardiogram Induced by Tilting. J. Lab. & Clin. Med. **33**:951 (Aug.), 1948.

In this study careful analysis has been made of the response of heart rate and blood pressure to tilting in normal subjects in order to establish a standard to evaluate changed reactions due to disease or drugs. This report details the findings in fifteen healthy young adults considered to have normal cardiovascular systems. The subjects were tilted at a moderate rate from the 20° head-up position to the 45° head-down position. This position was maintained for at least fifteen seconds and at least three sets of observations were made on each subject.

Elevation of arterial blood pressure in the arm occurred during the head-down tilt in all of the subjects studied. The average rise was 19 mm. Hg systolic and 16 mm. Hg diastolic. This was followed by a gradual fall lasting from eight to eighteen seconds until the blood pressure reached a level that was usually slightly higher than that obtained in the erect position. During the return to the head-up position, the blood pressure fell in all of the subjects, the fall averaging 14 mm. systolic and 13 mm. diastolic. The blood pressure returned to the starting level within eight to eighteen seconds of the completion of the tilt. Assumption of the head-down tilt position invariably caused slowing of the heart rate. With the head-up tilt position the heart rate suddenly increased following the drop in blood pressure. This resulted in a rate that was more rapid than the initial rate in this position in about one-half of the subjects.

The authors found that following the assumption of the 45° head-down position there resulted a slowing of the heart rate determined from prolongation of the P-R interval and in 20 per cent of normal subjects the P wave gradually decreased in size and finally disappeared for several beats. The disappearance of the P wave was not preceded by a shortening of the P-R interval. This change did not invariably occur in the same individual on successive tilting.

KLINE.

LeRoy, G. V., and Nalefsi, L. A.: Dicumarol in Experimental Myocardial Infarction. J. Lab. & Clin. Med. **33**:961 (Aug.), 1948.

The present study was undertaken to investigate the influence of Dicumarol therapy on the healing of experimental myocardial infarcts. Attention was directed particularly to: (1) the mortality rate after the administration of Dicumarol, (2) the extent and character of the infarct, grossly and microscopically, (3) the evolution of the electrocardiographic changes, and (4) the behavior of the sedimentation rate. The infarcts were produced by ligation of the anterior descending branch of the left coronary artery. Serial determinations of the prothrombin time, the hematocrit, the sedimentation rate, and serial electrocardiograms were made on all dogs. The animals were sacrificed at intervals of five to twenty-two days after the ligation of the coronary artery.

Seven of the thirty-two dogs died within twenty-four hours after the production of coronary occlusion, giving an immediate mortality of 21.8 per cent. Five of the dogs treated with Dicumarol developed complications as a result of the abnormal hemorrhagic tendency that resulted. There was no mural thrombosis in any animal, and there was no evidence that any thromboembolic phenomena occurred. Serial electrocardiograms did not show any consistent significant difference between the treated animals and the control animals. There did not appear to be any significant, consistent difference in the size of the infarcts or the amount of hemorrhagic infiltration in the two groups of animals. Microscopic examination of representative sections revealed no obvious difference between the healing infarctions in the treated animals and in the control animals. The variations in the sedimentation rate were not consistent and were of no importance in evaluating the course of experimental myocardial infarction.

The authors conclude that Dicumarol did not have any demonstrable deleterious influence on the healing of experimental myocardial infarction in dogs.

KLINE.

Balkin, S. S., and Gootnick, A.: The Effects of Dicumarol on the Electrocardiogram. J. Lab. & Clin. Med. **33**:972 (Aug.), 1948.

Dicumarol was given to forty-eight subjects. Of these, twelve were normal and sixteen had various types of cardiovascular disease with abnormal electrocardiographic patterns which remained stable during preliminary observation. In addition, fourteen patients with acute myocardial infarction who were on a Dicumarol regimen were studied. A separate group of six digitalized patients whose electrocardiograms had remained stable under prolonged observation were also treated with Dicumarol to observe the possible modifying influence of the drug on the several degrees of digitalis effect. Serial electrocardiograms, composed of Leads I, II, III, CF_3, CF_4, and CF_5 were taken in all subjects and were analyzed with respect to rhythm, auriculoventricular and intraventricular conduction, Q-T duration, RS-T level, and the amplitude of auricular and ventricular components. Dicumarol was given until the prothrombin level remained between 15 and 25 per cent of normal.

No significant electrocardiographic deviations attributable to Dicumarol were observed in any of the subjects.

KLINE.

Hauptmann, A., and Myerson, A.: Studies of Finger Capillaries in Schizophrenia and Manic-Depressive Psychoses. J. Nerv. & Ment. Dis. **108**:91 (Aug.), 1948.

The authors examined seventy-five individuals diagnosed as schizophrenics and subdivided as follows: forty-nine undoubted schizophrenics, ten schizophrenics with predominant paranoid symptoms, four schizophrenics with outstanding hallucinations, and twelve questionable schizophrenics. They examined thirty-seven patients in the manic-depressive group (thirty-two in a depressive state and five in a manic state) and three patients with other forms of psychoses. The total was 115 cases.

The mentally and emotionally "normal" individuals showed a normal structure of the capillaries of the fingernail fold. Mentally deficient children, whose retardation was not caused by

environmental factors, showed an immature, arrested picture of their finger capillaries. The capillary picture of the schizophrenics was quite different from that of the patients with manic-depressive manifestations. The main feature of the schizophrenics was an immature formation of the capillaries, whereas manic-depressives showed twisted capillaries.

The capillary picture of the schizophrenics was present in children prior to the end stage of the capillary development. The most pronounced immature pictures were found in those schizophrenics who showed all the classical clinical features of this disease. The rapidity of the development of the psychosis and its chronicity were not related to the capillary picture. Of the forty-nine undoubted schizophrenics, thirty-five (71.5 per cent) showed this typical immature picture. The capillary picture of the remaining fourteen patients was often partially immature; moreover, the clinical picture permitted some doubt in the diagnosis. These fourteen patients with schizophrenia with a nontypical, immature capillary picture stand very close to the group of twelve doubtful schizophrenics in respect to the capillary picture. The abnormal capillary picture in schizophrenics did not change during the course of the disease regardless of remission, new attacks, or electric shock treatments.

The capillary picture of the depressive or of the manic patients was markedly different from that of the schizophrenics. It was characterized by twisted capillaries. This capillary picture is the picture found in constitutional psychoneurotics. Of the thirty-two patients with depressive manifestations, twenty-four (75 per cent) showed this picture; of thirty-six patients with manic manifestations twenty-eight (78 per cent) had this characteristic capillary pattern.

In some cases the capillary picture corresponded better to the course of the psychosis than the clinical diagnosis made at the beginning of the illness. The clinical features of immaturity in schizophrenia find their bodily correlation in the immature capillary picture.

BELLET.

Mowbray, R., and Bowley, C. C.: Congenital Complete Heart Block Complicating Pregnancy. J. Obst. & Gynaec. Brit. Emp. **55**:438 (Aug.), 1948.

Three cases of congenital heart block complicating pregnancy are described and discussed. The authors point out that the most frequent associated anatomic defect is a patent interventricular septum, but heart block has also been described with pulmonary stenosis, aorto-pulmonary patency, dextrocardia, atrial septal defect, and other congenital abnormalities. In this condition the prognosis is usually good.

The authors were unable to find a case reported where congenital heart block and atrial septal defect complicated pregnancy, as in their first case. The second case was only diagnosed late in pregnancy after the bradycardia had been noticed in a prenatal clinic. It seemed probable that an interventricular defect was the associated anatomic abnormality in this case. The third patient was already known to be suffering from congenital heart block, but on the data available, it was impossible to state what the underlying anatomic condition was. The first two patients showed ventricular rates over 40 per minute, while the rate in the third patient varied from 32 to 72 beats per minute.

The third case illustrated the possible effect of a complicating toxemia of pregnancy with hypertension on an already abnormal heart. There seemed little doubt that in this case the cardiac failure from which the patient died was precipitated, not primarily by the pregnancy, but by the toxemia and hypertension. The second patient also showed a mild degree of toxemia in both her pregnancies which was insufficient in degree to affect the cardiac state adversely.

BELLET.

Williams, F., and Leonards, J. R.: The Effect of Sodium Bicarbonate on the Renal Excretion of Salicylate. J. Pharmacol. & Exper. Therap. **93**:401 (Aug.), 1948.

The authors demonstrated that bicarbonate had no effect on intestinal absorption of salicylates. However, in both the dog and man the renal excretion of salicylate was markedly increased by the administration of bicarbonate. This effect was more marked in the dog, as less of the salicylate was bound to the serum proteins and more passed through the glomerular filter. Bicarbonate

had no effect upon the binding of salicylate by the plasma proteins in either dog or man. The increase in excretion was due to an increased clearance value. In man the salicylate clearance was approximately equal to the urea clearance and with bicarbonate administration the salicylate clearance exceeded that of urea and actually approached the glomerular filtration rate.

The dose of bicarbonate used in man (5.0 to 7.0 Gm.) was in excess of the commonly used amounts in clinical medicine; furthermore, there were no prolonged determinations of salicylate blood levels with and without bicarbonate administration. However, the findings seemed to warrant further clinical evaluation.

GODFREY.

Short, D. W.: Occupational Aneurysm of the Palmar Arch. Lancet **255**:217 (Aug. 7), 1948.

Traumatic true aneurysms in the palm, due to repeated minor injuries, are very uncommon, approximately eleven cases having been reported. Most aneurysms of this type are associated with the ulnar artery and are found deep in the inner border of the hypothenar eminence. In the author's single case, the patient, a marine engineer, sought medical advice because of a tender lump in the right palm. As part of his daily duties, he shifted a stiff reversing lever by hammering it with the palm of his hand. After two months of this type of work, he noted increasing tenderness over the area and a slowly growing swelling. The tumor was not mobile or pulsatile and felt like a cyst. On operation it was found to be a saccular aneurysm arising from the superficial palmar arch immediately distal to the deep branch of the ulnar artery.

Generally, the symptom in this condition is a persistent bruised feeling, with a tender swelling appearing later. Sensory disturbances are sometimes prominent.

ABRAMSON.

Mathews, F. P.: Enterococcal Endocarditis. Northwest Med. **47**:581 (Aug.), 1948.

A 53-year-old mill worker was admitted to the hospital complaining of sore tongue, sore throat, and fever. A diagnosis of Ludwig's angina and rheumatic aortic stenosis was made. He had had rheumatic fever at 14 years of age and this had left him with a heart murmur. Ten days after admission the patient suddenly experienced severe substernal pain and the aortic murmur was found to have increased in intensity. The organism found in blood cultures was classified, on the basis of heat resistance, as an enterococcus, rather than as *Streptococcus viridans*.

A penicillin sensitivity test was performed on a subculture from the first blood culture. After forty-eight hours of incubation, growth was found to have been inhibited in the first two tubes but took place in three tubes of higher dilution. Accordingly, the penicillin dose, which had been begun at 20,000 units every four hours intravenously, was increased to 40,000 units every three hours. Two days later, following confirmation by the second blood culture, the dose was raised to 80,000 units every three hours. The neck symptoms cleared up and temperature gradually came down. Five weeks after admission the patient was discharged; at this time the only murmur present was the aortic systolic murmur which was present on admission. About one week later the patient was readmitted with marked dyspnea and return of substernal pain, The heart had apparently dilated further. The patient was digitalized and an oxygen tent applied, but signs of bronchospasm developed, and three days later the lungs became edematous and the patient died.

Necropsy revealed the immediate apparent cause of death to be an oval perforation through the posterior mitral valve leaflet, which was assumed to have taken place about a week before death, as its edges were partially healed.

The author points out that in this case of enterococcal endocarditis, the organism was sensitive to the bacteriostatic action of penicillin clinically and in vitro; because of the rupture of a mitral valve leaflet after the activity of the infectious process had apparently subsided, the case ended fatally.

BELLET.

Gover, M.: Variation of Blood Pressure and Heart Disease With Age, and the Correlation of Blood Pressure With Height and Weight. Pub. Health Rep. **63**:34 (Aug. 20), 1948.

This survey by the Farm Security Administration is the only large-scale study of an exclusively low-income rural group.

When the percentage of the population with hypertension is computed, comparative studies often use different standards. But regardless of the criteria of hypertension, allowance for the "normal increase in mean blood pressure with advanced age" is rarely made. The author notes that the percentage of persons with high blood pressure does not increase as rapidly with age as it does when computed from a base which is not age-specific.

The chief finding of the author is that age-specific mean systolic blood pressure for members of low-income farm families is higher than in recorded observations for other population groups, mainly urban; mean diastolic blood pressure for the farm group does not differ greatly from that recorded for urban groups.

Low-income rural men under 30 years of age had a relatively high prevalence of heart disease; in men over 30 the rural rates are similar to those of urban industrial workers. The systolic pressure had a small but significant correlation with weight.

WAIFE.

Macht, D. I.: Penicillin, Streptomycin, Dicumarol and Blood Coagulation; Thromboplastic Properties of Penicillin Antibiotics. South. M. J. **41**:720 (Aug.), 1948.

Experiments were made by the author using rabbits, cats, and dogs with injections of penicillin in various doses both intravenously and intramuscularly. He found that in all of the experiments such injections exerted thromboplastic effects. He studied the effect separately of the active principles of penicillin G, X, F, and K. He found that penicillin X was the most thromboplastic and that penicillin K was next in thromboplastic effectiveness. In experiments on rabbits and cats the author also found that the coagulation time was definitely shortened by streptomycin. The clot-promoting property of penicillin can be antagonized by the cautious administration of Dicumarol. He also found that in animals receiving large doses of Dicumarol which developed an extremely prolonged prothrombin and coagulation time with resultant hemorrhagic tendencies, the danger of hemorrhage can be effectively controlled by injections of penicillin.

The author concludes that clinically one must always be on guard against the added risk of thromboembolic accidents when administering antibiotics, especially in bacterial endocarditis where massive doses are used, and that heparin or Dicumarol should be administered in such cases. It was also found that x-ray increases the thromboplastic properties of penicillin.

KLINE.

Robb, J. S., Kaylor, C. T., and Turman, W. G.: A Study of Specialized Heart Tissue at Various Stages of Development of the Human Fetal Heart. Am. J. Med. **5**:324 (Sept.), 1948.

In this investigation four human fetal hearts were used. The fetuses from which the hearts were obtained were of 15½, 20, 21, and 32 weeks' gestation, respectively. In three of these hearts the S-A node was found to extend almost around the entire entrance of the superior vena cava into the right auricle. Pathways, uninterrupted by connective tissue, made connections from this node to the A-V node. One of these extended from the posterior portion of the S-A node in the sulcus terminalis, then along the posterior atrial wall, thence horizontally along the A-V junctional area to the A-V node. Another extended from the anterior portion of the S-A node, anterior to the foramen ovale, to the upper, somewhat posterior portion of the A-V node. Still other strands from the S-A node connected through the right and left portions of the interatrial septum to the more distal portions of the A-V node and proximal portions of the bundle. None of these pathways was composed exclusively of specialized tissue. On the contrary, specialized cells appeared near the nodes but then spread out to make end-to-end transitions into ordinary atrial muscle. The silver preparations of one heart indicated that there was a con-

siderable supply of nerve fibers to the S-A node and also to the A-V node, but because of the lack of a differential stain for sympathetic fibers, no observations were made on their course or terminations. From the A-V node compact bundles of specialized cells streamed distally forming the bundle of His, which divides into two main outflows at the top of the interventricular septum. The authors confirmed the previous observation that the left outflow appears as a broad, flat sheet which eventually separates into anterior, posterior, and septal portions. However, they report that the right outflow does not consist of one single limb, although it is usually in discrete bands and not "sheet-like," as on the left. Connections from the main bundle and from all parts of the right and left branches to septal muscle were seen in all of the hearts.

In general, the cells throughout the specialized system are alike and are different from either auricular or ventricular cells. It was found that the nodes are imbedded in connective tissue which is well differentiated with the Masson and Mallory stains. The bundle, its branches, and the Purkinje transitions into ordinary heart muscle are all enclosed in a connective tissue sheath. Nothing was found that could be considered to be an end organ. Whenever a Purkinje strand was followed peripherally it eventually underwent gradual transition into an ordinary heart muscle fiber. This transition was always arranged end-to-end. The authors did not find an accessory bundle of His although multiple A-V bridges of ordinary muscle tissue were observed.

KLINE.

Littmann, D.: Abnormal Electrocardiograms in the Absence of Demonstrable Heart Disease. Am. J. Med. 5:337 (Sept.), 1948.

This author reports nine cases which illustrate the occurrence of inverted T waves in precordial leads in individuals without demonstrable heart disease. They were selected from 5,000 electrocardiograms which were read over a period of eighteen months. With one exception, none of the patients had any complaints referable to the heart. In that one case the symptoms were considered to be due to a marked cardiac neurosis and aerophagia.

The electrocardiogram of the first case revealed the presence of alternating ventricular premature beats. In Lead IVF the T wave of the sinus beat was sharply inverted. After several days of rest fewer extrasystoles were noted. The electrocardiogram at this time showed T-wave inversion only in the beat which followed the extrasystole.

The second and third cases showed inverted T waves in Leads CF_2 and CF_3 in one case and inverted T waves in all of the CF leads in the other. In both cases, however, the T waves in CR leads were upright and of normal amplitude. These two cases were considered to represent persistence of the juvenile pattern in the electrocardiogram of adults.

The next four cases were grouped together because of several common features. The limb leads contained T-wave deviations which varied from lowering and flattening to frank inversion. The most marked abnormalities, however, were noted in the precordial leads. The greatest degree of T-wave inversion occurred in leads made at or near the apex. In all of these subjects essentially normal curves were obtained with the passage of time or following vigorous exercise. The author suggests that these patients represent instances of normal hearts with unstable T waves.

In the eighth case the electrocardiogram showed T-wave inversions in Leads CF_2, CF_3, and CF_4 and in CR_2 and CR_3. It later became apparent that the curves obtained in the morning before the patient had eaten were normal, while those made later in the day were abnormal. No significant changes were observed following exercise, hyperventilation, or the administration of atropine or prostigmine.

In the ninth case the inversion of the T waves in the CF leads was due to a proved mediastinal emphysema and pneumothorax.

The author stresses that the electrocardiogram should be regarded merely as one diagnostic procedure which is to be integrated with other findings.

KLINE.

Taran, L. M., and Szilagyi, N.: Oxygen Therapy in Acute Rheumatic Carditis in Children. Am. J. Med. 5:379 (Sept.), 1948.

Forty-four children, 7 to 16 years of age, presenting unequivocal evidence of acute rheumatic carditis, were treated in oxygen chambers for an average period of twelve weeks. Temperature was kept constant at a level of 66° to 68°F. and the humidity fluctuated between 60 and 70 per cent. Carbon dixoide concentration was permitted to rise to a level of 1.3 to 1.5 per cent. Other forms of cardiac therapy were instituted only when urgently indicated.

Twenty-four of the forty-four patients showed definite clinical improvement as a result of oxygen therapy as manifested by a marked and rapid drop in the heart rate and a decrease in respiratory rate. Precordial pain and evidence of cardiac fatigue subsided. In some instances there was an increase in diuresis and a significant drop in the previously elevated venous pressure. The tumultuous character of the heart action was changed to a quiet and slow rhythm. In addition, the clinical behavior of the patient was profoundly changed in favor of a more complete recovery. It was also noted that in the greater majority of the "responsive" patients there was an increase in appetite and weight along with improvement in facial coloring.

Seventeen of the forty-four treated children were not benefited by oxygen therapy. Most of these were advanced cardiacs with a long-standing carditis and evidence of minimal or severe heart failure. Three children could not tolerate oxygen therapy. They belonged to the "bronchitic" type of rheumatic carditis.

The authors observed that oxygen therapy did not alter the established anatomic cardiac damage but reduced significantly the cardiac functional disability which is present during the acute phase of the disease.

KLINE.

Taran, L. M., and Szilagyi, N.: Effect of Oxygen Therapy on the Electrical Sequence of Events in the Cardiac Cycle in Children With Acute Rheumatic Carditis. Am. J. Med. 5:392 (Sept.), 1948.

This paper reports the relationship of systole to diastole in children with acute carditis receiving oxygen therapy.

Fifteen girls, 10 to 14 years of age, were chosen for this study. All had unequivocal histories of rheumatic fever and during the period of observation had obvious clinical signs and symptoms of rheumatic carditis. All patients presented moderate to marked prolongation of the electrical systole (Q-T interval). During the entire period of observation no medication was given except an occasional sedative. None received digitalis for more than three weeks preceding the period of observation. After a control period of not less than two weeks these patients were introduced into an oxygen chamber where the oxygen concentration was 45 to 50 per cent and the carbon dixoide concentration level fluctuated between 1 and 1.3 per cent.

In all of the cases studied the cardiac rate was decreased and there was a rapid return to a more normal relationship of systole to diastole when oxygen therapy was begun. This was attained not by a significant shortening of the systolic period (Q-T) but rather by a marked lengthening of the diastolic period (T-Q). This occurred in all cases irrespective of the time it took to effect the result after oxygen therapy was instituted. All patients showed unequivocal clinical improvement as the electrical sequence of events approached a more normal relationship.

KLINE.

De Palma, A. F.: Scalenus Anticus Syndrome Treated by Surgery and Skeletal Traction. Am. J. Surg. 76:274 (Sept.), 1948.

The scalenus anticus syndrome is characterized by neurological and circulatory findings. The neurological findings consist of sensory symptoms in the form of paresthesia and pain along the flexor and ulnar surfaces of the forearm, shoulder, angle of the scapula, pectoral muscles, and often in the root of the neck and ear of the affected side. Later there may be muscular atrophy of the thenar eminence or of the interossei muscles.

The circulatory manifestations consist of decreased cutaneous temperature, numbness, and formication in the extremity and frequently cyanosis and puffiness of the hand and forearm and diminution of the radial pulse. Later trophic changes, to the point of gangrene of the finger tips, may intervene. Obliteration of the radial pulse can be produced by downward traction on the involved extremity or when the patient extends the cervical spine and rotates the head toward the affected side while taking a deep breath. A very common finding is tenderness in the supraclavicular fossa, especially over the distal third of the scalenus anticus muscle, lateral to the sternocleidomastoid muscle. The scalenus anticus muscle may be tense, contracted, and even hypertrophied.

The basis for these findings is a disturbance involving the brachial plexus and the subclavian vessels of the affected extremity. The nervous manifestations are the result of irritation of the brachial plexus, especially of its middle and lower trunks, causing spasm and contraction of the scalenus anticus muscle, which, in turn, results in an elevation of the first rib. As a consequence, greater stimulation of the plexus occurs, with perpetuation of the spasm of the muscle.

The cause of the vascular manifestations is not clear. They may be the result of stimulation of the sympathetic fibers in the lowest nerve trunk or of direct pressure on the brachial plexus and subclavian artery.

The predisposing factors which contribute to the initiation of the scalenus anticus syndrome may be the presence of a cervical rib, congenital anomalies of the cervical vertebrae and of the scalenus anticus muscle, and a postfixed brachial plexus. Among the exciting factors are the descent of the shoulders beyond normal limits in adulthood, pressure of the scalenus anticus muscle on the plexus during the period of greatest activity and muscular development, and poor posture involving an abnormal droop of the shoulder girdles.

The author believes that in the milder form of this syndrome conservative measures should be used in treatment. In the presence of poor posture, corrective exercises and some type of support to pull the shoulder girdle upward and backward will give considerable and prompt relief. When the syndrome is the result of direct or indirect trauma to the scalenus anticus muscle, rest to the part with the arm in an elevated position will also alleviate the symptoms. Repeated procaine injections into the muscle are worth while as an adjunct therapy.

When conservative measures fail, traction on the cervical spine or division of the scalenus anticus muscle may have to be performed. Traction is obtained by means of steel hooks inserted subperiosteally beneath the zygoma. Straight traction is made on the cervical spine by means of a 5- to 10-pound weight. Symptoms usually disappear within six to eight hours after traction has been applied, but this is maintained for ten days, after which the patient is made to wear a light cervical collar for two weeks. Of the author's sixteen patients treated by traction, all were relieved of pain, except one who had a recurrence of symptoms.

ABRAMSON.

Bageant, W. E., and Rapee, L. A.: The Treatment of Pulmonary Embolus by Stellate Block. Anesthesiology **8**:500 (Sept.), 1947.

The authors present two cases in which a stellate block was done for episodes of severe pulmonary embolism, with dramatic and immediate relief of chest pain, dyspnea, orthopnea, and cyanosis, and with a probable reversal of a shock syndrome.

A 36-year-old man was admitted to the hospital because of a severe grade of heart failure. He manifested shortness of breath and swelling of the feet and ankles. On the second hospital day auricular fibrillation developed. On the eighth hospital day quinidine was given for the fibrillation. The cardiac rhythm became regular, but on the fourteenth hospital day, the patient complained of a sudden onset of severe pain in the right lower chest. He had associated dyspnea, orthopnea, cyanosis, an elevation of temperature, marked apprehension, moderate sweating, and he expectorated a small amount of blood-tinged sputum. Later, a severe pain developed over the left chest as well. A stellate block was done on the right side with 2.5 c.c. of 2 per cent Metycaine, and after a typical Horner's syndrome appeared, 1.0 c.c. of a long-acting anesthetic agent in oil was injected. Within a few minutes the patient experienced almost complete relief of pain in the right chest and later also in the left chest. His breathing became easier, his chest

expansion greater, chest splinting was less, and he fell asleep for the first time since the onset of the pulmonary infarction. A roentgenogram confirmed the diagnosis of pulmonary infarction of the right chest. The patient remained comfortable until the twenty-second hospital day, when he had a second pulmonary embolus. A second stellate block was done immediately on the right side with 6.0 c.c. of 2 per cent Metycaine, and after a typical Horner's syndrome appeared, 1.0 c.c. of a long-acting anesthetic agent in oil was injected. He experienced almost immediate relief of his pain and dyspnea. The patient remained comfortable until the thirty-first hospital day, at which time he had his third pulmonary embolus. A stellate block was not done at this time, for he was semicomatose and he remained so until his death. Necropsy revealed rheumatic myocarditis with aortic stenosis and insufficiency, cardiac failure, multiple pulmonary infarcts of the right lung, and old multiple infarcts of the left lung.

The second case was that of a 39-year-old woman who was suddenly awakened with a severe, excruciating pain in the right chest. She was admitted to the hospital the same day. A roentgenogramconfirmed the clinical diagnosis of pulmonary embolism. A stellate block was done with 3.0 c.c. of 2 per cent Metycaine, and after a typical Horner's syndrome appeared, 1.0 c.c. of a long-acting anesthetic agent in oil was injected. After an interval of five minutes, the patient experienced marked relief of chest pain and was immediately able to breathe more freely and deeply. On the afternoon of this same date, under spinal anesthesia, the femoral veins were ligated, since these veins were considered to be the source of the embolus.

The authors state that blocking of the stellate ganglion interrupts the painful irritative impulses arising from the sympathetic nerves innervating the pulmonary vessels. This apparently breaks up the vicious cycle (pulmonary and/or coronary vascular spasm phenomena) by blocking the painful nerve impulses as stated and permitting vasodilatation of the pulmonary vessels. There is immediate relief of pain, dyspnea, orthopnea, and cyanosis; a greater chest expansion results and the state of shock is apparently reversed.

BELLET.

Blackman, N. S., and Hamilton, C. I., Jr.: Serial Electrocardiographic Changes in Young Adults With Acute Rheumatic Fever; Report of 62 Cases. Ann. Int. Med. **29**:416 (Sept.), 1948.

Sixty-two young white men, who had been admitted to the hospital with an initial episode of subacute or acute arthritis involving one or more joints, were studied with serial electrocardiograms in which only the three standard limb leads were used. In all members of this group, initial treatment consisted of bed rest and the administration 5 to 15 Gm. of sodium salicylate daily. Electrocardiograms were obtained every other day from the first week of hospitalization and twice each week thereafter.

Slightly over 40 per cent showed transitory prolongation of the P-R interval. In all instances prolongation of the P-R interval returned to normal before discharge. A transitory Wenckebach phenomenon was seen in one case. No instances of complete A-V heart block were recorded The Q-T interval was found to be prolonged in 35 per cent of the cases. In four of this number, it was the only demonstrable deviation from normal in the electrocardiogram. Two instances of wandering pacemaker were recorded. In addition, other disturbances of rhythm, such as auricular premature contractions, ventricular premature contractions, nodal rhythm, sinus bradycardia, and paroxysmal tachycardia, were occasionally observed.

Changes in the RS-T segment were chiefly confined to fluctuation in the elevation and depression of these segments and occurred in 22.5 per cent of the cases. Transient variations of the T wave were the most common abnormality noted. At one end of the scale were those cases with increased amplitude of the T wave and at the other end, those cases with deep inversion of the T wave. Between these two extremes were intermediate variations of this deflection. All of the 98.4 per cent of cases showing abnormalities in the serial records showed these changes within the first two weeks of the onset of the clinical symptoms. The implications of this last observation are discussed by the authors.

Emphasis is placed upon the fact that early in the course of the illness the diagnosis of rheumatic carditis frequently must depend upon changing electrocardiographic patterns in serial records.

WENDKOS.

Jones, H. E., and Marshall, A. G.: Isolated (Fiedler's) Myocarditis. Arch. Dis. Childhood **23**:201 (Sept.), 1948.

A fatal case of idiopathic (Fiedler's) myocarditis is described in a male infant who experienced no illness until 9 months of age, when he became fretful and refused food. For the subsequent weeks until death at 11 months he was pale, listless, and vomited on most days. He was never febrile. Two days following onset of symptoms he was given sulfonamide (amount unknown) for five days. Five weeks after onset he was hospitalized. The chief findings were slight cyanosis and cardiac and liver enlargement. He developed periodic attacks of dyspnea and died in a severe episode of dyspnea.

The main findings at autopsy were general dilatation of auricles and ventricles with a thickening of their walls and gross thickening of the endocardium of the left auricle. No valvular lesions were observed. Sections from auricles and ventricles, mitral valve, and papillary muscle all showed a diffuse infiltration of the myocardium by lymphocytes with little alteration of the muscle cells.

JOHNSON.

Wakim, K. G., Gersten, J. W., Herrick, J. F., Elkins, E. C., and Krusen, F. H.: The Effects of Diathermy on the Flow of Blood in the Extremities. Arch. Phys. Med. **29**:583 (Sept.), 1948.

The authors studied the effect of diathermy on the rate of peripheral circulation in a series of dogs and in a group of human subjects. Blood flow was determined in dogs by the use of a bubble flowmeter and in man, by the venous occlusion plethysmographic method.

The results indicated that diathermy produces a substantial increase in local circulation, particularly when applied directly to the extremity under study.

ABRAMSON.

Ziegler, R. F.: The Cardiac Mechanism During Anesthesia and Operation in Patients With Congenital Heart Disease and Cyanosis. Bull. Johns Hopkins Hosp. **83**:237 (Sept.), 1948.

The purpose of this study is to determine the mechanism, significance, and management of cardiac arrhythmias occurring during anesthesia and operation in children with congenital heart disease and cyanosis and to determine the preterminal cardiac mechanism in the children who die during this period. Patients selected for the study included 175 consecutive children with congenital heart disease and cyanosis submitted to the Blalock-Taussig operation for the correction of the abnormal circulatory dynamics of pulmonic stenosis with an intracardiac right-to-left shunt. Similar electrocardiographic records were made in a control group which included fifteen patients in whom a patent ductus arteriosus was ligated; three patients in whom coarctation of the aorta was corrected surgically; and two patients who underwent resection of the pericardium for constrictive pericarditis.

The general incidence of the disturbances of the cardiac mechanism during anesthesia and operation in this series of children with congenital heart disease and cyanosis was approximately the same as the incidence in the noncyanotic group, where cyclopropane was the chief anesthetic agent. The author confirms the statement that the anesthetic agent is of greater importance than the type of operative procedure in the production of cardiac irregularities.

Arrhythmias of some sort occurred in approximately 80 per cent of the entire group of patients. Sinus tachycardia was found to occur during all stages of operation and could be attributed in many instances to the effect of atropine given either as routine preoperative medication or during the course of anesthesia and operation. Sinus bradycardia was most frequently observed under circumstances apparently favoring vagal stimulation, as evidenced by the fact that it was abolished in most cases by the administration of atropine. Ectopic arrhythmias occurred in more than one-half of the children. In forty-six (52.3 per cent), the disturbance reverted spontaneously to normal sinus rhythm; in nineteen (21.6 per cent), reversion was accomplished with atropine; in eight (9.1 per cent), the disturbance was unaffected by atropine; and in fifteen (17 per cent), the arrhythmia could not be classified. Nodal rhythm of various types occurred with nearly equal frequency during anesthesia and throughout all phases of operation and was not related to any specific operative procedure.

While direct vagal stimulation, as in mediastinal exploration and manipulation of the great vessels, may be responsible for the occurrence of such arrhythmias, they may also result from action of the anesthetic agent acting by way of the vagus nerves, as well as directly upon the myocardium and the specialized tissues of the heart. Morphine tended to exaggerate the arrhythmias, in part perhaps, by vagal stimulation, and atropine in the amounts usually given failed to protect the heart against irregularities produced by morphine. Morphine is claimed to have a protective effect against ectopic arrhythmias such as cyclopropane-epinephrine tachycardia.

Arrhythmias due to increased cardiac irritability, including premature systoles and paroxysmal tachycardia, occurred in a total of twenty-one patients (13.3 per cent).

Another type of disturbance of the cardiac mechanism, which can be detected only by electrocardiography, is the group of abnormalities of the form of the ventricular deflections.

In the terminal group were included seven children who died during anesthesia or operation, two children who experienced several episodes of cardiac asystole on the operating table and who died within twenty-four hours of cerebral thrombosis probably occurring during asystole, and one additional child whose operation was postponed after he had survived what was thought to be a series of preterminal arrhythmias during anesthesia. The terminal cardiac mechanism in each of the seven cases was cardiac asystole. Ventricular fibrillation occurred only once and in this case only after a prolonged period of asystole.

In every case except one, sinus tachycardia with a rate of 150 to 200 per minute preceded the onset of any other abnormality of the cardiac mechanism. Of much greater significance was marked bradycardia, either sinus or A-V nodal, which occurred in every case prior to terminal asystole. It seems evident that bradycardia, either sinus or nodal, with a rate of less than 50 per minute and with failure to respond to the administration of atropine, constitutes a specific warning of impending terminal asystole.

The author suggests that anoxemia is a factor of considerable importance. In support of this concept is the low average arterial oxygen saturation in the terminal group and the occurrence of other electrocardiographic abnormalities known to depend upon myocardial anoxia, as in coronary insufficiency with or without myocardial infarction.

During anesthesia and operation, stagnant anoxia, which may result from a failing circulation and which may, in turn, further depress the heart and circulation, should be benefitted by the action of cardiac stimulants such as epinephrine and digitalis. Should the heart dilate and stop, intracardiac injection of epinephrine has been one of the most widely recommended procedures. The danger of precipitating fatal ventricular fibrillation, especially during cyclopropane anesthesia, has been emphasized. Electrocardiographic evidence of this cardiac mechanism as a cause of death has been lacking in most human subjects and in this present study ventricular fibrillation never occurred even after the administration of large amounts of epinephrine. Greater value may be expected from the administration of a longer acting specific cardiac stimulant, such as digitalis, or by supplying the heart with essential materials for energy production, such as available oxygen, respiratory enzymes, electrolytes, etc., at the same time that the circulation is maintained by manual massage or the rhythmical stimulation of an artificial pacemaker.

The three children in whom the most marked changes in QRS occurred all had more complicated malformations than a simple tetralogy of Fallot; all three had severe congestive heart failure following the systemic-pulmonary anastomosis; and two died in less than one year after operation, the third surviving perhaps only because of ligation of her artificial ductus.

BELLET.

Cahill, G. F.: Pheochromocytomas. J. A. M. A. **138**:180 (Sept. 18), 1948.

The author reviews his diagnostic and therapeutic experience with pheochromocytomas, presenting four of his cases in detail; he also discusses the observations of other investigators. He points out that although pheochromocytomas occur chiefly in the adrenal, they may also occur in pheochrome tissue in other parts of the body. Such extra-adrenal tumors occur intra-abdominally, for the most part, but instances of three such tumors located intrathoracically and one located intracranially have been reported. Although pheochromocytomas are seen particularly

in adults, with some predilection for females, a number have occurred in children. In nine per cent of cases in one series the tumors were considered to be malignant; in 9.7 per cent they were bilateral.

For diagnosis, the author places great faith in the benzodioxan test. This drug, 2-(1- piperidylmethyl)-1, 4- benzodioxan, is an epinephrine antagonist and when injected intravenously in the recommended dosage in cases of hypertension resulting from a pheochromocytoma, brings about a prompt and marked fall in the systolic and diastolic pressures with return to the prior pressure levels after fifteen minutes. No pressure changes occur with benzodioxan in hypertension of other types. The delineation of an adrenal pheochromocytoma radiographically with the aid of perirenal air insufflation for contrast and the x-ray demonstration of a tumor on urographic study are valuable diagnostic aids.

Surgical removal of the tumor is the only applicable therapeutic measure. Handling of the tumor before all its vessels have been ligated is dangerous because of the excessive quantities of epinephrine which may be expressed into the circulation. The intravenous use of epinephrine is of value when the drop in the blood pressure immediately following removal of a secreting tumor is of alarming magnitude, and adrenal cortical hormone may be needed if acute adrenocortical insufficiency results postoperatively. A rapid elevation of the systolic blood pressure to near its preoperative level within ten minutes after removal of a pheochromocytoma is an indication that a second functioning tumor is present.

HANNO.

Mendlowitz, M.: The Effect of Anemia and Polycythemia on Digital Intravascular Blood Viscosity. J. Clin. Investigation **27**:565 (Sept.), 1948.

The author studied four patients with polycythemia and two with marked anemia. Digital blood flow, vascular resistance, and blood pressure were determined with the object of measuring blood viscosity.

Anemia tended to decrease, while polycythemia tended to increase blood viscosity. At the extremes observed, the viscosity was 80 per cent of normal at a hematocrit of 17 and 169 per cent of normal at a hematocrit level of 73.

WAIFE.

Bloomfield, R. A., Rapoport, B., Milnor, J. P., Long, W. K., Mebane, J. G., and Ellis, L. B.: The Effects of the Cardiac Glycosides Upon the Dynamics of the Circulation in Congestive Heart Failure. J. Clin. Investigation **27**:588 (Sept.), 1948.

The newer techniques in cardiac physiology were used in a study of thirteen patients with varying degrees of heart disease in an attempt to determine the effects of the intracardiac injection of ouabain on the circulation. After venous catheterization ouabain was injected through the catheter over a period of one to two minutes in doses of 0.25 to 0.95 milligram.

In nine patients with clinical congestive failure, with low cardiac output, and an elevated right heart pressure the femoral arterial systolic pressure rose within a few minutes after ouabain injection, as did the mean and pulse pressures. Right ventricular and pulmonary arterial pressures were also increased. This group showed an increase in cardiac output. Peripheral venous pressure had not decreased at the time of the first increase in cardiac output in four of seven subjects so studied. In the other three patients circulatory pressure change had taken place before there was a drop in venous pressure.

In one to two hours variable pressure findings were noted which may be explained by alterations in blood volume or peripheral resistance. In three patients the cardiac output was unchanged or fell after ouabain. Two of these were not in clinical heart failure.

These authors conclude that ouabain acts directly on the failing heart by increasing its stroke volume; this action usually precedes cardiac slowing or any decrease in peripheral venous or right ventricular filling pressure.

WAIFE.

Book Reviews

THE CHEST AND THE HEART. By J. Arthur Myers, M.D., and C. H. McKinley, Ph.D. Springfield, Ill., 1948, Charles C Thomas, Publisher, 2 volumes, 1846 pages, with figures and tables. Price $25.50.

Although the title of this two-volume work, "The Chest and the Heart," would lead one to believe that one volume is devoted to diseases of the lungs and the other volume to diseases of the heart, such is not the case. Volume I deals with disease of the chest in 1,021 pages. In Volume II, 308 pages are devoted to nonpulmonary tuberculosis and only 329 pages to the heart. It is, therefore, no wonder that the material presented on diseases of the heart is sketchy and incomplete. No attempt has been made to follow the generally accepted diagnostic scheme of the American Heart Association; actually each chapter, usually by a different author, follows its own pattern. We have, then, in effect, a series of short individual monographs rather than an integrated presentation of diseases of the heart. In spite of the restrictions in space, some of the authors of individual sections have done a remarkably good job. The roentgenology of the heart is ably presented by Ungerlieder and Gubner. Photographs of models of the heart assist greatly in explaining the many excellent roentgenograms which illustrate the chapter. Chapters on the physiology of the heart by Visscher, on our present knowledge and research on arterial hypertension by Page, on coronary artery sclerosis by Barnes, and on the physiological aspects of the electrocardiogram by Ashman are among the highlights in the book.

There is no section on clinical electrocardiography. The subject of cardiac arrhythmias is poorly presented, the electrocardiograms are not clear, and the frequent use of poorly chosen case reports makes this section rather hard to read.

The treatment of heart failure rightly emphasizes the importance of rest and the necessity for digitalis. However, the author of this section does not appear to be familiar with the literature on cardiac glycosides, because he speaks of digitoxin, Digoxin, and lanatoside C together, as though they were indicated in the same situations. He seems unaware of the extremely long latent period of digitoxin, because he advocates this drug intravenously (p. 1750) along with the other glycosides for the treatment of acute left ventricular failure. Nowhere are the differences in latent period or rate of dissipation of the individual glycosides discussed.

The author also does not seem to know that theophylline is combined with all mercurial diuretics now used because of its local tissue-protecting action. He says nothing of the antidiuretic effect of morphine or Demerol. In discussing toxicity of mercurial diuretics, he omits the important point of possible idiosyncrasy to one of the mercurial diuretics, which, if not recognized, might lead to sudden death of the patient on the next injection.

Although the section on pulmonary surgery occupies twenty-five pages, cardiac surgery is dismissed quite casually in five pages.

It is evident that the editors of this book were primarily interested in diseases of the chest, and the section on the heart was added as an afterthought. This is indicated in their preface, where it is stated, "Originally this volume was intended to combine and bring to date two books published in 1927, namely, *The Normal Chest* and *Modern Aspects of the Diagnosis, Classification and Treatment of Tuberculosis*." Thus, we have an explanation of why tuberculosis of the genitourinary tract and even tuberculosis of the skin are forced into a book entitled "The Chest and the Heart." Since the heart is located in the chest, the editors were finally persuaded to in-

clude some discussion of the heart and grudgingly allowed less than one-fifth of the total space to the heart.

Since in the heart section there is much excellent material written by outstanding specialists in cardiology, it is hoped that a second edition will eliminate the sections on nonpulmonary tuberculosis from the second volume so that the entire second volume can be devoted to diseases of the heart. It is also hoped that the heart section will have its own editor (a cardiac specialist) who will be able to arrange the material so that there is included an adequate presentation of all phases of heart disease in an orderly and systematic manner. Some uniformity, then, will also apply as to bibliography. Now some sections, such as the section on arterial hypertension, are followed by an excellent, well-chosen set of references and others have no references at all.

ARTHUR C. DE GRAFF, M.D.

THE RENAL ORIGIN OF HYPERTENSION. By Harry Goldblatt, M.D. Springfield, Ill., 1948, Charles C Thomas, Publisher, 128 pages, 3 tables, and 38 figures. Price $2.75.

The purpose of the American Lecture Series is to provide at moderate cost and in lasting, pleasing form authoritative dissertations on special topics. Dr. Goldblatt's book, *Experimental Renal Hypertension*, admirably fulfills the publisher's intention.

The work is shaped along the same line as the author's recent survey in *Physiological Reviews*. As such, it has the good and bad qualities of style favored by that journal. The good lies in a thoroughgoing exposition and integration of the author's work and of his conclusions as they now stand. The disadvantage is not at all serious for those who intend further study. It lies in a neglect of the fact that other workers, as is the author, are entitled to revise their views as new facts present themselves. Consequently, those who intend to devote to the field more than a deliberate study of this single volume will find themselves being more critical than a wider review would justify.

The style is clear, the illustrations pleasing, the clinical comments well restrained, and the whole is recommended to all who intend to read still a little further.

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DR. H. M. MARVIN ELECTED PRESIDENT AT ANNUAL MEETING IN ATLANTIC CITY

Dr. H. M. Marvin, who has played a leading role in the affairs of the Association since its organization, was elected President for the 1949-1950 term at the Twenty-fifth Annual Meeting and Twenty-second Scientific Sessions held at the Haddon Hall, Atlantic City, the first week in June. Dr. Marvin, who is Associate Clinical Professor of Medicine at Yale University School of Medicine, succeeds Dr. Tinsley R. Harrison, of Dallas.

Chosen President-elect for the 1950-1951 term was Dr. Howard B. Sprague, of Boston, a former President of the New England Heart Association and member of the faculty of Harvard Medical School. Other officers elected are Dr. Edgar V. Allen, Rochester, Minn., Vice-president; Dr. John J. Sampson, San Francisco, Secretary (re-elected); and Grant Keehn, New York, Treasurer (re-elected).

At a meeting of the Board of Directors, A. W. Robertson, of Pittsburgh, was re-elected Chairman. Newly elected to the Board of Directors were: Arlie R. Barnes, M.D., Rochester, Minn.; Mrs. Douglas O. Burnham, Watertown, Conn.; George K. Fenn, M.D., Chicago, Ill.; Tinsley R. Harrison, M.D., Dallas, Texas; John C. Higgins, Vancouver, Wash.; T. Duckett Jones, M.D., New York, N. Y.; Louis N. Katz, M.D., Chicago, Ill.; Robert L. King, M.D., Seattle, Wash.; Rustin McIntosh, M.D., New York, N. Y.; Douglas B. Marshall, Houston, Texas; Frank L. Mechem, Seattle, Wash.; David D. Rutstein, M.D., Boston, Mass.; John J. Sampson, M.D., San Francisco, Calif.; Russell Stover, Kansas City, Mo.; C. J. Van Slyke, M.D., Washington, D. C.; Robert W. Wilkins, M.D., Boston, Mass.; Irving S. Wright, M.D., New York, N. Y.

The Annual Membership Meeting which named the officers of the Association (Board members are chosen by the Assembly) also elected the following to the Assembly, the over-all governing body which includes both lay and medical members:

Listed regionally:

New England

O. Kelley Anderson, Boston, Mass.
Julian Anthony, Boston, Mass.
Laurence D. Chapin, M.D., Springfield, Mass.
Paul K. French, M.D., Burlington, Vt.
John H. Frye, Jr., Portland, Maine
Marshall N. Fulton, M.D., Providence, R. I.
Vlado A. Getting, M.D., Boston, Mass.
John H. Miller, M.D., Laconia, N. H.
Henry Utter, M.D., Providence, R. I.

East

James N. Brittain, Philadelphia, Pa.
Irvin M. Cook, Baltimore, Md.
Albert D. Kaiser, M.D., Rochester, N. Y.
Charles A. Poindexter, M.D., New York, N. Y.

South

Harold Green, M.D., Winston-Salem, N. C.
Arthur Grollman, M.D., Dallas, Texas
Edgar Hull, M.D., New Orleans, La.
Douglas Marshall, Houston, Texas
George R. Meneely, M.D., Nashville, Tenn.
John F. Phillips, Albany, Ga.
William C. Stewart, M.D., Charleston, W. Va.
C. J. Van Slyke, M.D., Washington, D. C.
Wallace M. Yater, M.D., Washington, D. C.

Great Lakes

Claude E. Beck, M.D., Cleveland, Ohio
Alva Bradley, Cleveland, Ohio
John F. Briggs, M.D., Minneapolis, Minn.
S. J. Collins, Youngstown, Ohio

Kurt Stubenvoll, Eau Claire, Wis.
Stanley Dorst, M.D., Cincinnati, Ohio
A. Carlton Ernstene, M.D., Cleveland, Ohio
Herman C. Krannert, Indianapolis, Ind.
Sidney Strauss, M.D., Chicago, Ill.
Charles E. Wilson, Detroit, Mich.

Midwestern and Mountain

Clarence Beck, Emporia, Kan.
John Lucien Calene, M.D., Aberdeen, S. D.
Hans H. Hecht, M.D., Salt Lake City, Utah
Palmer Hoyt, Denver, Colo.
Fred G. Jenkins, Kansas City, Mo.
Robert N. Larimer, M.D., Sioux City, Iowa
Frederick W. Niehaus, M.D., Omaha, Neb.
Russell Stover, Kansas City, Mo.

West

John Martin Askey, M.D., Los Angeles, Calif.
Philip Bailey, Seattle, Wash.
Max Hemingway, M.D., Bend, Ore.
S. P. Lucia, M.D., San Francisco, Calif.
Robert C. Manchester, M.D., Seattle, Wash.
E. B. McNaughton, Portland, Ore.
Donald S. Munroe, M.D., Vancouver, B. C.
S. M. Poindexter, M.D., Boise, Idaho
John W. Scott, M.D., Edmonton, Alberta
Donal R. Sparkman, M.D., Seattle, Wash.

GOLD AWARDS GIVEN AT ANNUAL DINNER

The Atlantic City sessions included Annual Meetings of the Scientific Council and of its Section on the Circulation, as well as of the American Council on Rheumatic Fever. Preceding these was a two-day organization meeting of the Staff Conference of Heart Associations, a newly formed group comprising the professional staff workers in the affiliates of the American Heart Association.

Two Scientific Sessions, followed by three panel discussions, were held at which nineteen papers were presented and a number of others were read by title only. Dr. George E. Burch, New Orleans, was Chairman of the panel discussion on Management of Congestive Failure and Importance of Low Sodium Diet. A second panel on Congenital Heart Disease was presided over by Dr. Alfred Blalock, Baltimore. Dr. Edgar V. Allen, Rochester, Minn., was Chairman of the panel on Anticoagulant Therapy.

The newly created Gold Award, symbolized by a certificate and a gold medallion in the form of the Association's symbol, was presented at the Annual Dinner to nine major contributors to the success of the 1949 National Campaign.

Harold E. Stassen, President of the University of Pennsylvania and National Campaign Chairman in 1949, was the first recipient of the Gold Award, presented to him by Dr. Marvin, the incoming President. Mr. Stassen in turn presented Gold Awards to William E. Cotter, Executive Vice-chairman of the February campaign; Mark Woods, Chairman of the Public Relations Committee; Sylvester L. Weaver, Jr., Chairman of the Radio and Television Committee, and Raoul E. Desvernine, Chairman of the Men's Committee. Recipients of the Gold Award in absentia were Miss Irene Dunne, Women's Committee Chairman; Maurice J. Tobin, Secretary of Labor, Chairman of the Labor Committee; Juan T. Trippe, Chairman of the Corporations Committee, and Ralph Edwards, of the "Truth or Consequences" radio program.

Representative Walter H. Judd, Member of Congress from Minnesota and also a physician, addressed the Annual Dinner on "Trends in International Affairs." Mr. Stassen gave an interim report on the 1949 National Campaign and announced that $2,850,000 had been raised at the time of the Annual Meeting, with additional increments expected.

The Staff Conference of Heart Associations was addressed at its organizational meeting by Professor Ira V. Hiscock, Chairman of the Department of Public Health, Yale University School of Medicine, and by Dr. Alan Gregg, Director for the Medical Sciences, Rockefeller Foundation.

AMERICAN LEGION AID CITED AT MEETING OF AMERICAN COUNCIL ON RHEUMATIC FEVER

The generous action of the American Legion and the American Legion Auxiliary in lending valuable assistance to the Association at a critical time was high-lighted at the annual meeting of the American Council on Rheumatic Fever. In a résumé of the Council's activities since January 1, 1948, special attention was given to the American Legion Fund of $50,000, contributed jointly by the Legion and Auxiliary at a time in 1946 when the grant served as a catalyzing agent to stimulate broadening of the Association program.

It was reported that the fund was fully expended or allocated as of February 28, 1949. One-half of the fund ($25,000) was utilized in two three-year fellowships granted to Dr. Joseph E. Warren, of the House of the Good Samaritan, Boston, and Dr. Samuel T. Schlamovitz, New York University College of Medicine, for research in rheumatic fever. Dr. Warren has subsequently been awarded a research fellowship by the Association for continuation of his studies. Reports by both American Legion fellows were presented at the Atlantic City meeting.

The remainder of the Legion Fund was expended for staff assistance, permitting continuity of operation of the Council during a difficult period of reorganization of the American Heart Association.

BOARD APPROVES $6,000,000 GOAL FOR 1950; HAWAII HEART ASSOCIATION ADMITTED TO AHA

The Executive Committee of the Board of Directors at its April meeting approved a proposed budget for 1950 which included plans for a 1950 fund-raising campaign with a goal of $6,000,000.

The Board voted to amend the Association's certificate of incorporation to permit activity in "other related fields of medicine and research or through other health organizations." The permissible number of Directors was also raised to 100, with by-law change to set the actual number at sixty instead of forty as at present.

The President was authorized to appoint a committee to study the possibilities of effecting a merger with the Society for the Study of Arteriosclerosis as a Section of the Scientific Council of the American Heart Association.

The Association's farthest-away affiliate was admitted to the AHA family with the Board's approval of the application of the Hawaii Heart Association.

COURSE IN ELECTROCARDIOGRAPHY

The annual intensive two-week course in electrocardiography for *graduate physicians* will be given at Michael Reese Hospital in Chicago, under the personal direction of Dr. Louis N. Katz, Director of Cardiovascular Research, from August 15 to August 27, 1949, inclusive. Group and individual instruction will be given, and the course is open to beginning and advanced students in electrocardiography. The course will meet daily from 8:00 A.M. to 5:00 P.M. Tuition fee is $150.00.

Further information and a copy of the lecture schedule may be obtained on application to Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, Twenty-ninth Street and Ellis Avenue, Chicago 16, Illinois.